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TO: Everett White **Location: REM/5D24** **Art Unit: 1623** **Monday, March 22, 2004** **Case Serial Number: 10/686,918**	**From: Mary Jane Ruhl** **Location: Biotech-Chem Library** **Remsen 1-B55** **Phone: 571-272-2524** **maryjane.ruhl@uspto.gov**

5C18

Search Notes

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Mary Jane Ruhl
Technical Information Specialist
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CM-1, Rm. 6-A-06
605-1155

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=> d que stat l18
L1             1 SEA FILE=REGISTRY ABB=ON  "CHONDROITIN SULFATE"/CN
L2             1 SEA FILE=REGISTRY ABB=ON  N-ACETYL-D-GLUCOSAMINE/CN
L3             1 SEA FILE=REGISTRY ABB=ON  HYALURONAN/CN
L5         27033 SEA FILE=HCAPLUS ABB=ON  L1 OR L2 OR L3 OR ?CHONDROITIN?(W)?SUL
                 FATE? OR (CS4 OR CS6)(W)?CHONDROITIN?(W)?SULFATE? OR N(W)?ACETY
                 L?(W)D(W)?GLUCOSAMINE? OR ?HYALURONAN?
L7             0 SEA FILE=HCAPLUS ABB=ON  L5 AND ?CARTILAG?(4A)?DIATHROD?(W)?JOI
                 NT?
L11          893 SEA FILE=HCAPLUS ABB=ON  L5 AND (?JOINT?(W)(?LAVAGE? OR
                 ?TREATMENT?) OR ?ARTHRITIS? OR ?DEGEN?(W)?JOINT?(W)?DISEAS?)
L12          893 SEA FILE=HCAPLUS ABB=ON  L7 OR L11
L13          245 SEA FILE=HCAPLUS ABB=ON  L5 AND (?SYNOV?(W)?MEMBRAN? OR
                 ?SYNOVITIS?)
L14         1013 SEA FILE=HCAPLUS ABB=ON  L12 OR L13
L15          403 SEA FILE=HCAPLUS ABB=ON  L14 AND (?JOINT?(W)?CARTILAG? OR
                 ?ARTICUL?)
L16           86 SEA FILE=HCAPLUS ABB=ON  L15 AND (?METHOD? OR ?PROCED?)
L18           13 SEA FILE=HCAPLUS ABB=ON  L16 AND (?INTRAARTICUL? OR ?INTRAMUS?
                 OR ?INTRAVEN? OR IA OR IM OR IV)

=> d ibib abs l18 1-13

L18  ANSWER 1 OF 13  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:        2004:126909  HCAPLUS
TITLE:                   Effects of different molecular weight elastoviscous
                         hyaluronan solutions on articular
                         nociceptive afferents
AUTHOR(S):               Gomis, Ana; Pawlak, Matthias; Balazs, Endre A.;
                         Schmidt, Robert F.; Belmonte, Carlos
CORPORATE SOURCE:        Instituto de Neurociencias de Alicante, Universidad
                         Miguel Hernandez-CSIC, San Juan de Alicante, 03550,
                         Spain
SOURCE:                  Arthritis & Rheumatism (2004), 50(1), 314-326
                         CODEN: ARHEAW; ISSN: 0004-3591
PUBLISHER:               John Wiley & Sons, Inc.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Objective. To compare 3 different hyaluronan (HA) prepns. used
     as therapeutic agents for osteoarthritis pain in humans in order
     to establish the degree to which a single application affects the
     sensitivity of nociceptors in both the normal and the acutely inflamed rat
     joint. Methods. In anesthetized rats, single-unit recordings
     were performed from the medial articular nerve of the right knee
     joint under normal conditions and during an acute exptl. arthritis
     . Fifty fine afferent units (conduction velocities 0.8-15.3 m/s)
     responded to passive movements of the knee joint. They were exposed to a
     torque meter-controlled, standardized stimulus protocol consisting of
     innocuous and noxious inward and outward rotations of the joint. This
     stimulus protocol of 50 s' duration was repeated every 5 min for 2-3 h.
     Three com. available HA prepns. and a buffer solution, the solvent of these
     prepns., were injected intraarticularly after discharges
     resulting from 6 stimulus protocols were averaged and used as controls.
     Results. Both in normal and in inflamed joints, the injection of Hyalgan
     did not reduce nerve impulse frequency of the evoked discharges. The
     injections of Orthovisc had no effect in normal joints, but produced a
     transient frequency reduction of the evoked discharge in inflamed joints.
     Synvisc significantly reduced (by an average of 50%) the impulse discharge in
     both normal and inflamed joints 50 min after injection, and this level of
     impulse discharge continued until the end of the recording period (120-130
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min after injection). The buffer, which had elastoviscous properties substantially different from those of Hyalgan, Orthovisc, and Synvisc, had no such effect. Conclusion. We conclude that the elastoviscous properties of HA solns. are determining factors in reducing pain-eliciting nerve activity both in normal and in inflamed rat joints.

L18 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:875121 HCAPLUS
DOCUMENT NUMBER: 139:358758
TITLE: **Method** for treating inflammatory disorders
INVENTOR(S): Ganu, Vishwas Sadashiv; Hu, Shou-Ih; Kimble, Earl F.
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis Pharma G.m.b.H.
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003090758	A1	20031106	WO 2003-EP4342	20030425

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR

PRIORITY APPLN. INFO.: US 2002-375935P P 20020426
AB Disclosed herein are **methods** for treating inflammatory disorders, compns. for treating inflammatory disorders, and **methods** for identifying compds. that will treat inflammatory disorders. Production of inflammatory cytokines and non-cytokine inflammatory mediator mols. is inhibited and the amount of matrix metalloprotease activity is decreased by administering an effective amount of an inhibitor of N-glycosylation of proteins, wherein the inhibitor is not glucosamine and some other specified compds. Production of TNFα by IC-21 cells stimulated with LPS was inhibited by 2-deoxy-2-fluoro-d-glucose, 2-deoxy-2-fluoro-d-mannose and 2-deoxy-d-glucose.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:511513 HCAPLUS
DOCUMENT NUMBER: 139:63367
TITLE: Oligomer-based **method** of modulating the release of saccharides, and therapeutic uses thereof
INVENTOR(S): Boucher, Isabelle; Brunet, Serge
PATENT ASSIGNEE(S): ISM Biopolymer Inc., Can.
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2003054208 A2 20030703 WO 2002-CA1917 20021212
WO 2003054208 A3 20031009
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2001-339339P P 20011213

AB The invention provides a **method** for the controlled release of saccharides and oligosaccharides in humans and animals. Polysaccharides are digested in a manner to provide oligomers having desired nos. of units of saccharides or monosaccharides, most **particularly** glucosamine and N-acetylglucosamine and derivs. thereof. The rate of release of monosaccharides is proportional to the length of the oligomers administered to an organism, and has targeted physiol. effects depending on the length of the oligomers used. The **methodol**. and compns. of the invention are useful for the delayed delivery of chondroprotective, chondrosynthesis-stimulating agents.

L18 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:9703 HCAPLUS
DOCUMENT NUMBER: 138:49884
TITLE: The availability of highly elastoviscous hylan for viscosupplementation can delay knee replacement in patients with advanced **osteoarthritis**
AUTHOR(S): Weiss, C.; Waddell, D.; Miller, E.
CORPORATE SOURCE: Mount Sinai Medical Center of Greater Miami, Miami Beach, FL, 33141, USA
SOURCE: Hyaluronan, [Proceedings of the International Cellucon Conference], 12th, Wrexham, United Kingdom, 2000 (2002), Meeting Date 2000, Volume 2, 391-395. Editor(s): Kennedy, John F. Woodhead Publishing Ltd.: Cambridge, UK.
CODEN: 69DKVZ; ISBN: 1-85573-570-9
DOCUMENT TYPE: Conference
LANGUAGE: English

AB An anal. was performed to determine how viscosupplementation influences the need for knee replacement surgery in orthopedic practice. A total of 989 patients (1366 knees), in three clin. practices were treated with hylan G-F20 over a two-year period. The patients had advanced **osteoarthritis** (predominantly Kellgren and Lawrence X-ray Grade **IV**) and severe symptoms/disability. Most patient knees (82%) received a single 3-injection course of treatment. The majority of patients were clin. improved for 6 mo or longer. No significant systemic adverse reactions were observed, and local reactions occurred at a rate of 2-3% per injection, similar to other intra-**articular procedures**. The response to the second course of treatment was found to be similar to that of the first course in terms of safety and effectiveness. The rate of knee replacement in patients at all three clin. sites was significantly reduced compared to historical controls. Interestingly, Health Care Utilization Data from the United States similarly reflect declined national rates of knee replacement since the introduction of viscosupplementation. These data demonstrate that viscosupplementation with hylan G-F20 is an effective treatment for patients with advanced knee **osteoarthritis** that may postpone

knee replacement surgery in certain patients.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:773380 HCAPLUS
DOCUMENT NUMBER: 138:313659
TITLE: Potential mechanism of action of intra-**articular hyaluronan** therapy in **osteoarthritis**: are the effects molecular weight dependent?
AUTHOR(S): Ghosh, Peter; Guidolin, Diego
CORPORATE SOURCE: Institute of Bone and Joint Research, Department of Surgery, Royal North Shore Hospital, University of Sydney, New South Wales, Australia
SOURCE: Seminars in Arthritis and Rheumatism (2002), 32(1), 10-37
CODEN: SAHRBF; ISSN: 0049-0172
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Background: **Hyaluronan**, or hyaluronic acid (HA), is the major hydrodynamic nonprotein component of joint synovial fluid (SF). Its unique viscoelastic properties confer remarkable shock absorbing and lubricating abilities to SF, while its enormous macromol. size and hydrophilicity serve to retain fluid in the joint cavity during **articulation**. HA restricts the entry of large plasma proteins and cells into SF but facilitates solute exchange between the synovial capillaries and cartilage and other joint tissues. In addition, HA can form a pericellular coat around cells, interact with proinflammatory mediators, and bind to cell receptors, such as cluster determinant (CD)44 and receptor for hyaluronate-mediated motility (RHAMM), where it modulates cell proliferation, migration, and gene expression. All these physicochem. and biol. properties of HA have been shown to be mol. weight (MW) dependent. Objective: intra-**articular** (**IA**) HA therapy has been used for the treatment of knee **osteoarthritis** (OA) for more than 30 yr. However, the mechanisms responsible for the reported beneficial clin. effects of this form of treatment remain contentious. Furthermore, there are a variety of pharmaceutic HA prepns. of different MW available for the treatment of OA, but the significance of their MWs with respect to their pharmacol. activities have not been reviewed previously. The objective of the present review is to redress this deficiency. **Methods**: the authors reviewed in vitro and in vivo reports to identify those pharmacol. activities of HA that were considered relevant to the ability of this agent to relieve symptoms and protect joint tissues in OA. Where possible, reports were selected for inclusion when the pharmacol. effects of HA had been studied in relation to its MW. In many studies, only a single HA preparation had been investigated. In these instances, the exptl. outcomes reported were compared with similar studies undertaken with HAs of different MWs. Results: Although in vitro studies have generally indicated that high MW-HA prepns. were more biol. active than HAs of lower MW, this finding was not confirmed using animal models of OA. The discrepancy may be partly explained by the enhanced penetration of the lower MW HA preparation through the extracellular matrix of the synovium, thereby maximizing its concentration and facilitating its interaction with target synovial cells. However, there is accumulating exptl. evidence to show that the binding of HAs to their cellular receptors is dependent on their mol. size; the smaller HA mol. species often elicits an opposite cellular response to that produced by the higher MW prepns. Studies using large animal models

of OA have shown that HAs with MWs within the range of 0.5 + 106-1.0 + 106 Da were generally more effective in reducing indexes of synovial inflammation and restoring the rheol. properties of SF (visco-induction) than HAs with MW > 2.3 + 106 Da. These exptl. findings were consistent with light and electron microscopic studies of **synovial membrane** and cartilage biopsy specimens obtained from OA patients administered 5 weekly **IA** injections of HA of MW = 0.5 + 106-0.73 + 106 Da in which evidence of partial restoration of normal joint tissue metabolism was obtained. Conclusions: By mitigating the activities of proinflammatory mediators and pain producing neuropeptides released by activated synovial cells, HA may improve the symptoms of OA. In addition, HAs within the MW range of 0.5 + 106-1.0 + 106 Da partially restore SF rheol. properties and synovial fibroblast metabolism in animal models. These pharmacol. activities of HA could account for the reported long-term clin. benefits of this OA therapy. However, clin. evidence has yet to be described to support the animal studies that indicated that HAs with MW > 2.3 + 106 Da may be less effective in restoring SF rheol. than HAs of half this size.

REFERENCE COUNT: 184 THERE ARE 184 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:697982 HCAPLUS

DOCUMENT NUMBER: 137:383688

TITLE: Cartilage-specific constitutive expression of TSG-6 protein (product of tumor necrosis factor α-stimulated gene 6) provides a chondroprotective, but not antiinflammatory, effect in antigen-induced **arthritis**

AUTHOR(S): Glant, Tibor T.; Kamath, Rajesh V.; Bardos, Tamas; Gal, Istvan; Szanto, Sandor; Murad, Yanal M.; Sandy, John D.; Mort, John S.; Roughley, Peter J.; Mikecz, Katalin

CORPORATE SOURCE: Rush-Presbyterian-St. Luke's Medical Center, Rush University, Chicago, IL, USA

SOURCE: Arthritis & Rheumatism (2002), 46(8), 2207-2218 CODEN: ARHEAW; ISSN: 0004-3591

PUBLISHER: John Wiley & Sons, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Objective. To study the chondroprotective effect of constitutively expressed TSG-6 protein (tumor necrosis factor α-induced protein 6; Tnfip6) in cartilage, using antigen-induced **arthritis** (AIA) in mice. **Methods**. Transgenic mice constitutively expressing TSG-6 protein in cartilage were generated. Cartilage-specific constitutive expression of TSG-6 protein was confirmed by in situ hybridization, Western blot anal., and immunohistochem. Control and transgenic mice were immunized with methylated bovine serum albumin (mBSA), and **arthritis** was induced by the **intraarticular** injection of mBSA. Mice were monitored up to day 35 after the challenge, and knee joint sections were examined for loss of cartilage proteoglycan (aggrecan) using Safranin O staining and antibodies to neoepitopes generated by various metalloproteinases (MPs). The loss of aggrecan in Safranin O-stained sections was quantified by morphometric **methods**. Results. Tsg6/tnfip6 transgenic mice constitutively expressed tsg6/tnfip6 mRNA and corresponding TSG-6 protein in cartilage from embryonic life through adulthood, without any phenotypic abnormalities. These mice were used for AIA studies. **Intraarticular** injection of mBSA uniformly induced severe inflammation both in control (wild-type and an

irrelevant transgenic line) mice and in tsg6/tnfip6 transgenic mice. In contrast to the mBSA-injected knee joints of control animals that were heavily damaged from day 5, the cartilage of transgenic mice that constitutively expressed TSG-6 protein remained intact for at least 1 wk, and this was followed by a relatively reduced loss of aggrecan. Concomitant with the loss of aggrecan, MP-generated neoepitopes accumulated in unprotected joints. By day 35, the proteoglycan content returned to nearly normal levels in tsg6/tnfip6 transgenic mice, whereas it remained low in MP-damaged knee cartilage of control mice. Conclusion. TSG-6 protein is known to form a complex with inter-α-inhibitor (IαI), a potent serine protease inhibitor, which may be immobilized via the **hyaluronan** (HA)-binding domain of TSG-6 protein in the HA-rich extracellular matrix of cartilage. Thus, the local accumulation of TSG-6 protein and TSG-6 protein-bound IαI in tsg6/tnfip6 transgenic mice may inhibit serine proteases and subsequent activation of MPs. It is suggested that this mechanism might protect cartilage from extensive degradation even in the presence of acute inflammation.

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:584542 HCAPLUS
DOCUMENT NUMBER: 136:236773
TITLE: **Hyaluronan** molecular weight and polydispersity in some commercial intra-**articular** injectable preparations and in synovial fluid
AUTHOR(S): Adam, N.; Ghosh, P.
CORPORATE SOURCE: Institute of Bone and Joint Research, Department of Surgery, Royal North Shore Hospital, University of Sydney, St. Leonards, 2065, Australia
SOURCE: Inflammation Research (2001), 50(6), 294-299
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective and Design: **Hyaluronan** is the major non-proteinaceous component of joint synovial fluid and is responsible for the unique rheol. and biol. properties of this medium. In joint arthropathies the mol. weight and concentration of **hyaluronan** may change, thereby influencing joint physiol. and function. Intra-**articular** administered **hyaluronan** derived from a number of sources, has been used for the treatment of **osteoarthritis**, however, there is limited information on the mol. weight and polydispersity of these various com. prepns. The objective of this study was to develop an accurate, convenient **method** by which the mol. weight and polydispersity of **hyaluronan** may be determined and then applied to characterize the **hyaluronan** in synovial fluid. Materials and **Methods**: Characterization of the mol. parameters of **hyaluronan** of different sources and in ovine synovial fluid was accomplished by a multi-angle laser-light scattering (MALLS) detector coupled to a gel permeation chromatog. (GPC) system, fitted with an automatic sample injector. Conclusion: Seven com. available **hyaluronan** prepns. of reported mol. weight were analyzed. The weight average mol. weight (Mw) and number average mol. weight (Mn) values obtained for 6 of the 7 prepns. using the MALLS-GPC system were in good agreement with the reported values. The abnormally low values for the exception suggested that degradation of **hyaluronan** had occurred. The MALLS-GPC technique was then used to determine the mol. characteristics of the endogenous **hyaluronan** in normal ovine

synovial fluids. While the Mws ranged from <1 + 106 to 7 + 106 Da, the majority were between 1 + 106-3 + 106 Da. The effects of freezing and thawing synovial fluid upon mol. weight of **hyaluronan** were also investigated and were found to diminish both Mz and Mw values.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:607959 HCAPLUS
DOCUMENT NUMBER: 134:51164
TITLE: Amelioration of disease severity by **intraarticular** hylan therapy in bilateral canine **osteoarthritis**
AUTHOR(S): Marshall, K. W.; Manolopoulos, V.; Mancer, K.; Staples, J.; Damyanovich, A.
CORPORATE SOURCE: Division of Orthopaedics, The Toronto Hospital Arthritis Centre, Toronto, ON, M5T 2S8, Can.
SOURCE: Journal of Orthopaedic Research (2000), 18(3), 416-425
CODEN: JOREDR; ISSN: 0736-0266
PUBLISHER: Journal of Bone and Joint Surgery, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Because of its high mol. weight, the glycosaminoglycan mol. **hyaluronan** is responsible for the viscoelastic properties of normal synovial fluid. In **osteoarthritis**, the concentration and mol. weight of **hyaluronan** in synovial fluid is diminished; this impairs the ability of synovial fluid to effectively lubricate joints, absorb loads, and exert anti-inflammatory effects. Using a bilateral anterior cruciate-ligament transection and partial neurectomy canine model of **osteoarthritis**, this study examined the effect of visco-supplementation with hylan G-F 20 as a treatment for **osteoarthritis**. Twelve dogs underwent bilateral arthroscopic anterior cruciate-ligament transections and partial neurectomy of the knee joints. Beginning 1 wk after the operation, six dogs received three weekly 500-μl injections of hylan G-F 20 in one knee and a sham injection of saline solution in the contralateral knee (early-treatment group). The remaining six animals underwent the same treatment 2 mo following the **procedure** (late-treatment group). All dogs were killed at 8 mo, and both knees were evaluated for gross pathol., histol., and proteoglycan content. In addition, with use of 500-MHz [1H] magnetic resonance spectroscopy, the synovial fluid from both knees was assessed for changes in metabolic profile. Gross pathol. and histol. examination revealed significantly less severe changes of **osteoarthritis** in knees treated with hylan G-F 20 2 mo after surgery than in the contralateral untreated knees. Magnetic resonance spectroscopy of the specimens in this late-treatment group showed significantly decreased glucose concns. and significantly elevated isoleucine levels in the synovial fluid from knees treated with hylan G-F 20 compared with the controls. Previous magnetic resonance spectroscopy had shown that glucose concns. increase with the onset of **osteoarthritis** and eventually diminish in end-stage **osteoarthritis**. The three injections of hylan were given after **osteoarthritis** was established, and the severity of the disease was ameliorated in the treated knees 6 mo after treatment. This occurred although hylan G-F 20 is almost certainly cleared from joints by lymphatics within 4 wk of injection, suggesting that hylan therapy can retard the progression of **osteoarthritis** for periods of time extending beyond the **intraarticular** residence time of the injected mols. and that hylan injections given at relatively early stages of **osteoarthritis** may have a

chondroprotective effect. No changes in outcome were noted in the animals that received hylan G-F 20 immediately following surgery.
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:383192 HCAPLUS
DOCUMENT NUMBER: 133:190886
TITLE: Interaction of **intraarticular** **hyaluronan** and albumin in the attenuation of fluid drainage from joints
AUTHOR(S): Scott, D.; Coleman, P. J.; Mason, R. M.; Levick, J. R.
CORPORATE SOURCE: St. George's Hospital Medical School, London, SW17 0RE, UK
SOURCE: Arthritis & Rheumatism (2000), 43(5), 1175-1182 CODEN: ARHEAW; ISSN: 0004-3591
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: How is fluid volume regulated in joints. Fluid drainage rate is an important factor, both in normal joints and those with effusions. **Hyaluronan** and albumin, sep., are known to attenuate drainage, conserving synovial fluid volume in the presence of raised joint pressure. **Hyaluronan** and albumin normally coexist, however, in joint fluid. The objective was to determine their interactive effect on drainage. **Methods**: The fluid escape rate from the joint cavity through synovium was measured at controlled **intraarticular** pressures using a rabbit knee model in vivo. One joint contained 4 mg/mL **hyaluronan** and the other contained 4 mg/mL **hyaluronan** plus 20 mg/mL albumin, as in normal synovial fluid. **Hyaluronan** -albumin interactions were assessed in vitro by viscometry and osmometry. Results: **Hyaluronan** alone greatly attenuated fluid escape. Drainage rates plateaued at 4-5 μl/min as pressure was raised because the opposition to drainage increased with pressure. Addition of albumin to **hyaluronan** shifted the opposition-vs.-pressure relation upward and further attenuated drainage by 22.5% despite a small fall in the viscosity of the mixture Osmometry showed a small synergistic interaction. Anal. of aspirates showed that ≤8% of albumin mols. in the draining fluid were reflected by the synovial lining (compared with 79% of **hyaluronan** mols.). Conclusion: **Hyaluronan** and albumin act together at normal concns. to conserve synovial fluid in the presence of raised drainage pressures. **Hyaluronan** has the greater effect, acting osmotically by way of a concentration polarization boundary layer.
Attenuation of this effect in arthritic effusions with low **hyaluronan** concns. is one of several factors limiting fluid accumulation and, hence, the size of the effusion.
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:169160 HCAPLUS
DOCUMENT NUMBER: 131:27263
TITLE: The pathobiology of **osteoarthritis** and the rationale for the use of pentosan polysulfate for its treatment
AUTHOR(S): Ghosh, Peter
CORPORATE SOURCE: Institute of Bone and Joint Research, Royal North Shore Hospital of Sydney, St Leonards, 2065, Australia
SOURCE: Seminars in Arthritis and Rheumatism (1999), 28(4),

211-267
CODEN: SAHRBF; ISSN: 0049-0172
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 390 refs. Structure-modifying **osteoarthritis** (OA) drugs (SMOADs) may be defined as agents that reverse, retard, or stabilize the underlying pathol. of OA, thereby providing symptomatic relief in the long-term. The objective of this review was to evaluate the literature on sodium pentosan polysulfate (NaPPS) and calcium pentosan polysulfate (CaPPS), with respect to the pathobiol. of OA to ascertain whether these agents should be classified as SMOADs. Published studies on NaPPS and CaPPS were selected on the basis of their relevance to the known pathobiol. of OA, which also was reviewed. Both NaPPS and CaPPS exhibit a wide range of pharmacol. activities. Of significance was the ability of these agents to support chondrocyte anabolic activities and attenuate catabolic events responsible for loss of components of the cartilage extracellular matrix in OA joints. Although some of the anti-catabolic activities may be mediated through direct enzyme inhibition, NaPPS and CaPPS also have been shown to enter chondrocytes and bind to promoter proteins and alter gene expression of matrix metalloproteinases and possibly other mediators. In rat models of **arthritis**, NaPPS and CaPPS reduced joint swelling and inflammatory mediator levels in pouch fluids. Moreover, synoviocyte biosynthesis of high-mol.-weight **hyaluronan**, which is diminished in OA, was normalized when these cells were incubated with NaPPS and CaPPS or after **intraarticular** injection of NaPPS into arthritic joints. In rabbit, canine, and ovine models of OA, NaPPS and CaPPS preserved cartilage integrity, proteoglycan synthesis, and reduced matrix metalloproteinase activity. NaPPS and CaPPS stimulated the release of tissue plasminogen activator (t-PA), superoxide dismutase, and lipases from vascular endothelium while concomitantly decreasing plasma levels of the endogenous plasminogen activator inhibitor PAI-1. The net thrombolytic and lipolytic effects exhibited by NaPPS and CaPPS may serve to improve blood flow through subchondral capillaries of OA joints and improve bone cell nutrition. In geriatric OA dogs, NaPPS and CaPPS reduced symptoms, as well as normalized their thrombolytic status, threshold for platelet activation, and plasma triglyceride levels. These hematol. parameters were shown to be abnormal in OA animals before drug treatment. Similar outcomes were observed in OA patients when CaPPS or NaPPS were given orally or parenterally in both open and double-blind trials. The data presented in this review support the contention that NaPPS and CaPPS should be classified as SMOADs. However, addnl. long-term clin. studies employing **methods** of assessing joint structural changes will be needed to confirm this view.

REFERENCE COUNT: 391 THERE ARE 391 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:531141 HCAPLUS
DOCUMENT NUMBER: 119:131141
TITLE: Effects of **intraarticular hyaluronan** on matrix changes induced in the lateral meniscus by total medial meniscectomy and exercise
AUTHOR(S): Hope, Nigel; Ghosh, Peter; Taylor, Thomas K. F.; Sun, Dechang; Read, Richard
CORPORATE SOURCE: Raymond Purves Bone Jt. Res. Lab., North Shore Hosp., St Leonards, Australia
SOURCE: Seminars in Arthritis and Rheumatism (1993), 22(6, Suppl. 1), 43-51

CODEN: SAHRBF; ISSN: 0049-0172
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Total medial meniscectomy was performed in 12 adult merino sheep. Immediately after surgery, 8 animals received high-mol.-weight **hyaluronan** (HA) (1 mL, 10 mg/mL) and 4 were given sterile saline (1 mL) **intraarticularly**. Injections were given for 5 more weeks. In week 3 an exercise program, consisting of walking 24 km/wk, was initiated. This program was continued until the animals were killed at week 26 postmeniscectomy. At necropsy the lateral menisci were removed and divided into three concentric zones-inner, middle, and outer. Powdered aliquots of tissues from each zone were analyzed for collagen and hexuronate contents using colorimetric **methods**. The glycosaminoglycans (GAGs)-chondroitin-O-sulfate (C-O-S), chondroitin-4-sulfate (C-4-S), chondroitin-6-sulfate (C-6-S), and dermatan sulfate (DS)-were determined using a high performance liquid chromatog. **method**. The lateral menisci from the joints of animals injected with HA showed higher hexuronate and GAG levels than those of controls. This increase was mainly due to C-6-S, which had highest levels in the inner and middle meniscal zones. In addition, dermatan sulfate levels increased significantly in the middle and outer zones of the lateral menisci compared with the same zones of the meniscus from the saline-treated group. Collagen and C-O-A levels were not statistically different from those of controls. These data suggest that **intraarticular** administration of high-mol.-weight HA immediately after open total medial menisectomy may help preserve the proteoglycans in the lateral meniscus remaining in the joint.

L18 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1964:93274 HCAPLUS
DOCUMENT NUMBER: 60:93274
ORIGINAL REFERENCE NO.: 60:16332d-e
TITLE: Synovial proliferation induced by polysaccharides
AUTHOR(S): Thomas, D. D. Page; Dingle, J. T.; Cook, E. R.
SOURCE: Nature (London, United Kingdom) (1960), 186(4720), 251-2
From: CZ 1961(4), 1271.
CODEN: NATUAS; ISSN: 0028-0836
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB After an **intraarticular** injection of 2-3 mg. carrageenan (I), there occurs in the rabbit joint an increasing or decreasing proliferation of synovia, discernible in the increased number of synovial cells per unit area and in the mitotic index. Weekly injections of I lead to massive synovial proliferation, granulation formation, and matrix erosion of the **joint cartilage**. Glycogen, fucoidin, **chondroitin sulfate**, dextrin, starch, and pectic acid induced no such effects, while alginic acid and agar, even if in less volume than I, were active. The agarose component of agar was inactive; the agaropectin component showed the same effects as I; it also contains galactose and 3,6-anhydrogalactose, as well as sulfate and glyceric acid and pyruvic acids. This **method** of inducing synovial changes can be used in testing the antiproliferative characteristics of therapeutic substances.

L18 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1959:24396 HCAPLUS
DOCUMENT NUMBER: 53:24396
ORIGINAL REFERENCE NO.: 53:4509d-g
TITLE: Synovial fluid hyaluronate in rheumatoid

arthritis
AUTHOR(S): Hamerman, David; Schuster, Hilda
CORPORATE SOURCE: Albert Einstein Coll. Med., New York, NY
SOURCE: Arthritis Rheumatism (1958), 1, 523-31
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB cf. C.A. 52, 5599g. Two **methods** were used to determine hyaluronate (I) concentration of synovial fluids: (1) precipitation of I by glacial HOAc and estimation as hexosamine, and (2) digestion of fluids by hyaluronidase, followed by dialysis and estimation of the fall in hexosamine. Results of the 2 **methods** were in agreement. Mean I hexosamine of normal fluids was 1.4 mg./g.; in cases of rheumatoid **arthritis** whose fluid vols. exceeded normal, 0.4 mg./g. In normal fluids I hexosamine constituted 85% of the total hexosamine; in rheumatoid fluids only 30%. Increased amts. of plasma proteins in rheumatoid fluids presumably account for the large amount of non-I hexosamine. When normal and pathol. fluids were diluted with buffer to a I hexosamine concentration of 0.25 mg./g. relative viscosities of rheumatoid fluids were either similar, or in most cases only slightly lower, than normal. Thus, contrary to other reports, the degree of polymerization of I in rheumatoid **arthritis** is not appreciably decreased. **Intraarticular** injection of hydrocortisone reduced fluid vols. 70-90% and increased I concns., but did not increase the relative viscosities of equivalently diluted fluids.

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=> d que stat l22
L1             1 SEA FILE=REGISTRY ABB=ON  "CHONDROITIN SULFATE"/CN
L2             1 SEA FILE=REGISTRY ABB=ON  N-ACETYL-D-GLUCOSAMINE/CN
L3             1 SEA FILE=REGISTRY ABB=ON  HYALURONAN/CN
L5         27033 SEA FILE=HCAPLUS ABB=ON  L1 OR L2 OR L3 OR ?CHONDROITIN?(W)?SUL
                 FATE? OR (CS4 OR CS6)(W)?CHONDROITIN?(W)?SULFATE? OR N(W)?ACETY
                 L?(W)D(W)?GLUCOSAMINE? OR ?HYALURONAN?
L7             0 SEA FILE=HCAPLUS ABB=ON  L5 AND ?CARTILAG?(4A)?DIATHROD?(W)?JOI
                 NT?
L11          893 SEA FILE=HCAPLUS ABB=ON  L5 AND (?JOINT?(W)(?LAVAGE? OR
                 ?TREATMENT?) OR ?ARTHRITIS? OR ?DEGEN?(W)?JOINT?(W)?DISEAS?)
L12          893 SEA FILE=HCAPLUS ABB=ON  L7 OR L11
L13          245 SEA FILE=HCAPLUS ABB=ON  L5 AND (?SYNOV?(W)?MEMBRAN? OR
                 ?SYNOVITIS?)
L14         1013 SEA FILE=HCAPLUS ABB=ON  L12 OR L13
L15          403 SEA FILE=HCAPLUS ABB=ON  L14 AND (?JOINT?(W)?CARTILAG? OR
                 ?ARTICUL?)
L16           86 SEA FILE=HCAPLUS ABB=ON  L15 AND (?METHOD? OR ?PROCED?)
L18           13 SEA FILE=HCAPLUS ABB=ON  L16 AND (?INTRAARTICUL? OR ?INTRAMUS?
                 OR ?INTRAVEN? OR IA OR IM OR IV)
L19          244 SEA L18
L20          188 DUP REMOV L19 (56 DUPLICATES REMOVED)
L21           52 SEA L20 AND (INFLAM? OR POST?(W) SURG?)
L22           49 SEA L21 AND (THERAP? OR PREVENT? OR TREAT?)

=> d ibib abs l22 1-49

L22  ANSWER 1 OF 49     MEDLINE on STN
ACCESSION NUMBER:   2004028965     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 14730630
TITLE:              Effects of different molecular weight elastoviscous
                    hyaluronan solutions on articular
                    nociceptive afferents.
AUTHOR:             Gomis Ana; Pawlak Matthias; Balazs Endre A; Schmidt Robert
                    F; Belmonte Carlos
CORPORATE SOURCE:   Instituto de Neurociencias de Alicante, Universidad Miguel
                    Hernandez-CSIC, San Juan de Alicante, Spain.. agomis@umh.es
SOURCE:             Arthritis and rheumatism, (2004 Jan) 50 (1) 314-26.
                    Journal code: 0370605. ISSN: 0004-3591.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:        200402
ENTRY DATE:         Entered STN: 20040121
                    Last Updated on STN: 20040218
                    Entered Medline: 20040217
AB   OBJECTIVE: To compare 3 different hyaluronan (HA) preparations
     used as therapeutic agents for osteoarthritis pain in
     humans in order to establish the degree to which a single application
     affects the sensitivity of nociceptors in both the normal and the acutely
     inflamed rat joint. METHODS: In anesthetized rats,
     single-unit recordings were performed from the medial articular
     nerve of the right knee joint under normal conditions and during an acute
     experimental arthritis. Fifty fine afferent units (conduction
     velocities 0.8-15.3 meters/second) responded to passive movements of the
     knee joint. They were exposed to a torque meter-controlled, standardized
     stimulus protocol consisting of innocuous and noxious inward and outward
     rotations of the joint. This stimulus protocol of 50 seconds' duration
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was repeated every 5 minutes for 2-3 hours. Three commercially available HA preparations and a buffer solution, the solvent of these preparations, were injected **intraarticularly** after discharges resulting from 6 stimulus protocols were averaged and used as controls. RESULTS: Both in normal and in **inflamed** joints, the injection of Hyalgan did not reduce nerve impulse frequency of the evoked discharges. The injections of Orthovisc had no effect in normal joints, but produced a transient frequency reduction of the evoked discharge in **inflamed** joints. Synvisc significantly reduced (by an average of 50%) the impulse discharge in both normal and **inflamed** joints 50 minutes after injection, and this level of impulse discharge continued until the end of the recording period (120-130 minutes after injection). The buffer, which had elastoviscous properties substantially different from those of Hyalgan, Orthovisc, and Synvisc, had no such effect. CONCLUSION: We conclude that the elastoviscous properties of HA solutions are determining factors in reducing pain-eliciting nerve activity both in normal and in **inflamed** rat joints.

L22 ANSWER 2 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003182172 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12701040
TITLE: Intra-**articular** **hyaluronans**: a review of product-specific safety profiles.
AUTHOR: Hamburger Max I; Lakhanpal Sharad; Mooar Pekka A; Oster David
CORPORATE SOURCE: Rheumatology Associates of Long Island, Melville, NY 11747, USA.
SOURCE: Seminars in arthritis and rheumatism, (2003 Apr) 32 (5) 296-309. Ref: 51
Journal code: 1306053. ISSN: 0049-0172.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030418
Last Updated on STN: 20030827
Entered Medline: 20030826

AB BACKGROUND AND OBJECTIVES: Intra-**articular** (**IA**) **hyaluronans** (HAs) are indicated for pain relief of **osteoarthritis** (OA) of the knee. Hyalgan (sodium hyaluronate), Supartz (sodium hyaluronate), and Synvisc (hylan G-F 20) are Food and Drug Administration-approved HA products. They are derived from rooster combs; Hyalgan and Supartz are naturally derived (unmodified); Synvisc is chemically modified to increase its molecular weight. This article reviews and updates the safety data for **IA** HAs used for the **treatment** of knee OA. **METHODS**: References were taken from Medline through July 2002; respective product information services and information from the searchable United States Food and Drug Administration Manufacturer and User Facility Device Experience Database also were used. RESULTS: All products demonstrated favorable safety profiles in clinical trials and practice compared to other standard **therapies** for management of OA knee pain. The most common adverse event associated with HAs is mild injection site pain and swelling. Each product has had rare reports of pseudogout and anaphylactoid reactions. Product-specific adverse events, severe acute **inflammatory** reactions (pseudoseptic knee), in patients receiving Synvisc have been reported. One such patient developed antibodies to chicken proteins and

hylan, suggesting an immunologic basis for the severe acute **inflammatory** reaction. Data from an animal study support a possible immunogenic difference between Synvisc and Hyalgan. CONCLUSIONS AND RELEVANCE: Overall, HA **therapy** is a safe **treatment** for OA knee pain, although there may be interproduct variability in safety profiles.

L22 ANSWER 3 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2002703163 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12465161
TITLE: Are there distinctive **inflammatory** flares after hylan g-f 20 **intraarticular** injections?.
AUTHOR: Pullman-Mooar Sally; Mooar Pekka; Sieck Marie; Clayburne Gilda; Schumacher H Ralph
CORPORATE SOURCE: MCP/Hahneman University School of Medicine, Philadelphia, Pennsylvania, USA.
SOURCE: Journal of rheumatology, (2002 Dec) 29 (12) 2611-4. Journal code: 7501984. ISSN: 0315-162X.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20021217
Last Updated on STN: 20030508
Entered Medline: 20030507

AB OBJECTIVE: This survey was designed to examine features of a group of patients with acute painful joint effusions following hylan G-F 20 (Synvisc) knee injections. **METHODS**: Eight patients with painful local reactions after **intraarticular** hylan G-F 20 injections for knee **osteoarthritis** were evaluated clinically, with detailed synovial fluid analysis, and followed for outcome. RESULTS: Leukocyte counts ranged from 3150 to 103,000/mm3. Crystals were seen in one patient. **Inflammatory** knee effusions occurred from 1 to 48 h after injections, but never with first injections. Synovial fluid volumes were 30 to 71 mm(3). Three patients had shiny clumps (not further characterized) that were noted in leukocytes on Wright stained smears. Most patients were **treated** with aspiration and depot steroids. Five of the 8 patients had moderate or greater improvement at 6 months. CONCLUSION: The majority of the occasional dramatic episodes of **inflammation** after hylan G-F 20 injection do not seem to be related to crystals. No detrimental lasting results were noted. The absence of post-hylan flares following the first **intraarticular** injection in this small series suggests that sensitization to or accumulation of hylan G-F 20 or its breakdown products may play an etiologic role in these flares.

L22 ANSWER 4 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2002460295 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12219318
TITLE: Potential mechanism of action of intra-**articular** **hyaluronan** **therapy** in **osteoarthritis**: are the effects molecular weight dependent?.
AUTHOR: Ghosh Peter; Guidolin Diego
CORPORATE SOURCE: Institute of Bone and Joint Research, Department of Surgery, University of Sydney, Royal North Shore Hospital, New South Wales, Australia.. pghosh@mail.usyd.edu.au
SOURCE: Seminars in arthritis and rheumatism, (2002 Aug) 32 (1)

10-37. Ref: 181
Journal code: 1306053. ISSN: 0049-0172.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20020910
Last Updated on STN: 20030521
Entered Medline: 20030520

AB BACKGROUND: **Hyaluronan**, or hyaluronic acid (HA), is the major hydrodynamic nonprotein component of joint synovial fluid (SF). Its unique viscoelastic properties confer remarkable shock absorbing and lubricating abilities to SF, while its enormous macromolecular size and hydrophilicity serve to retain fluid in the joint cavity during **articulation**. HA restricts the entry of large plasma proteins and cells into SF but facilitates solute exchange between the synovial capillaries and cartilage and other joint tissues. In addition, HA can form a pericellular coat around cells, interact with proinflammatory mediators, and bind to cell receptors, such as cluster determinant (CD)44 and receptor for hyaluronate-mediated motility (RHAMM), where it modulates cell proliferation, migration, and gene expression. All these physicochemical and biologic properties of HA have been shown to be molecular weight (MW) dependent. OBJECTIVE: Intra-**articular** (**IA**) HA **therapy** has been used for the **treatment** of knee **osteoarthritis** (OA) for more than 30 years. However, the mechanisms responsible for the reported beneficial clinical effects of this form of **treatment** remain contentious. Furthermore, there are a variety of pharmaceutic HA preparations of different MW available for the **treatment** of OA, but the significance of their MWs with respect to their pharmacologic activities have not been reviewed previously. The objective of the present review is to redress this deficiency. **METHODS**: We reviewed in vitro and in vivo reports to identify those pharmacologic activities of HA that were considered relevant to the ability of this agent to relieve symptoms and protect joint tissues in OA. Where possible, reports were selected for inclusion when the pharmacologic effects of HA had been studied in relation to its MW. In many studies, only a single HA preparation had been investigated. In these instances, the experimental outcomes reported were compared with similar studies undertaken with HAs of different MWs. RESULTS: Although in vitro studies have generally indicated that high MW-HA preparations were more biologically active than HAs of lower MW, this finding was not confirmed using animal models of OA. The discrepancy may be partly explained by the enhanced penetration of the lower MW HA preparation through the extracellular matrix of the synovium, thereby maximizing its concentration and facilitating its interaction with target synovial cells. However, there is accumulating experimental evidence to show that the binding of HAs to their cellular receptors is dependent on their molecular size; the smaller HA molecular species often elicits an opposite cellular response to that produced by the higher MW preparations. Studies using large animal models of OA have shown that HAs with MWs within the range of 0.5 x 10(6)-1.0 x 10(6) Da were generally more effective in reducing indices of synovial **inflammation** and restoring the rheological properties of SF (visco-induction) than HAs with MW > 2.3 x 10(6) Da. These experimental findings were consistent with light and electron microscopic studies of **synovial membrane** and cartilage biopsy specimens obtained from OA patients administered 5 weekly **IA** injections of HA of MW = 0.5 x 10(6)-0.73 x 10(6) Da in which

evidence of partial restoration of normal joint tissue metabolism was obtained. CONCLUSIONS: By mitigating the activities of proinflammatory mediators and pain producing neuropeptides released by activated synovial cells, HA may improve the symptoms of OA. In addition, HAs within the MW range of 0.5 x 10(6)-1.0 x 10(6) Da partially restore SF rheological properties and synovial fibroblast metabolism in animal models. These pharmacologic activities of HA could account for the reported long-term clinical benefits of this OA **therapy**. However, clinical evidence has yet to be described to support the animal studies that indicated that HAs with MW > 2.3 x 10(6) Da may be less effective in restoring SF rheology than HAs of half this size.

L22 ANSWER 5 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2002451509 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12209527
TITLE: Cartilage-specific constitutive expression of TSG-6 protein (product of tumor necrosis factor alpha-stimulated gene 6) provides a chondroprotective, but not antiinflammatory, effect in antigen-induced **arthritis**.
AUTHOR: Glant Tibor T; Kamath Rajesh V; Bardos Tamas; Gal Istvan; Szanto Sandor; Murad Yanal M; Sandy John D; Mort John S; Roughley Peter J; Mikecz Katalin
CORPORATE SOURCE: Rush University, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois 60612, USA.. tglant@rush.edu
CONTRACT NUMBER: AR-40310 (NIAMS)
AR-45652 (NIAMS)
AR-47135 (NIAMS)
SOURCE: Arthritis and rheumatism, (2002 Aug) 46 (8) 2207-18. Journal code: 0370605. ISSN: 0004-3591.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020906
Last Updated on STN: 20020920
Entered Medline: 20020919

AB OBJECTIVE: To study the chondroprotective effect of constitutively expressed TSG-6 protein (tumor necrosis factor alpha-induced protein 6; Tnfip6) in cartilage, using antigen-induced **arthritis** (AIA) in mice. **METHODS**: Transgenic mice constitutively expressing TSG-6 protein in cartilage were generated. Cartilage-specific constitutive expression of TSG-6 protein was confirmed by in situ hybridization, Western blot analysis, and immunohistochemistry. Control and transgenic mice were immunized with methylated bovine serum albumin (mBSA), and **arthritis** was induced by the **intraarticular** injection of mBSA. Mice were monitored up to day 35 after the challenge, and knee joint sections were examined for loss of cartilage proteoglycan (aggrecan) using Safranin O staining and antibodies to neoepitopes generated by various metalloproteinases (MPs). The loss of aggrecan in Safranin O-stained sections was quantified by morphometric **methods**. RESULTS: Tsg6/tnfip6 transgenic mice constitutively expressed tsg6/tnfip6 messenger RNA and corresponding TSG-6 protein in cartilage from embryonic life through adulthood, without any phenotypic abnormalities. These mice were used for AIA studies. **Intraarticular** injection of mBSA uniformly induced severe **inflammation** both in control (wild-type and an irrelevant transgenic line) mice and in tsg6/tnfip6 transgenic mice. In contrast to the mBSA-injected knee joints of control animals

that were heavily damaged from day 5, the cartilage of transgenic mice that constitutively expressed TSG-6 protein remained intact for at least 1 week, and this was followed by a relatively reduced loss of aggrecan. Concomitant with the loss of aggrecan, MP-generated neoepitopes accumulated in unprotected joints. By day 35, the proteoglycan content returned to nearly normal levels in tsg6/tnfip6 transgenic mice, whereas it remained low in MP-damaged knee cartilage of control mice. CONCLUSION: TSG-6 protein is known to form a complex with inter-alpha-inhibitor (IalphaI), a potent serine protease inhibitor, which may be immobilized via the **hyaluronan** (HA)-binding domain of TSG-6 protein in the HA-rich extracellular matrix of cartilage. Thus, the local accumulation of TSG-6 protein and TSG-6 protein-bound IalphaI in tsg6/tnfip6 transgenic mice may inhibit serine proteases and subsequent activation of MPs. It is suggested that this mechanism might protect cartilage from extensive degradation even in the presence of acute **inflammation**.

L22 ANSWER 6 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2002420794 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12175098
TITLE: Comparison of the effects of intra-**articular** injections of **Hyaluronan** and its chemically cross-linked derivative (Hylan G-F20) in normal rabbit knee joints.
AUTHOR: Schiavinato A; Finesso M; Cortivo R; Abatangelo G
CORPORATE SOURCE: Department of Histology, Microbiology and Medical Biotechnologies, University of Padua, Italy.
SOURCE: Clinical and experimental rheumatology, (2002 Jul-Aug) 20 (4) 445-54.
Journal code: 8308521. ISSN: 0392-856X.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20020815
Last Updated on STN: 20030117
Entered Medline: 20030116

AB OBJECTIVE: **Intraarticular** injection of native **hyaluronan** (HA) or a cross-linked derivative are commonly utilized in the **treatment** of **osteoarthritis**. Unlike from native **hyaluronan**, the crosslinked HA derivative is a gel containing also other chemical entities. This study compares the local tolerability of these different preparations in normal rabbit knees, in order to provide further information on their biological effects. **METHODS:** Synovial fluids were aspirated after single or repeated weekly injections (up to three) of the **therapeutic** agents and cell count was determined in a Burker chamber and in an automatic cell counter. The percentage of the different cell types was determined by light microscopy in semithin sections of fixed synovial fluid cytocentrifugate. Fragments of **synovial membrane** were also morphologically analyzed. RESULTS: In the **synovial membrane** no signs of **inflammation** were evident either after a single or repeated injections of native **Hyaluronan** (Hyalgan or Artz). In addition, the cell recruitment and the percentage of cell types in the synovial fluid was not statistically different from saline **treated** joints. After 3 weekly injections of the crosslinked HA derivative (Hylan G-F20, Synvisc) about 50% of the **treated** joints appeared slightly **inflamed** and in these joints a statistically significantly higher cell content was determined in the synovial fluid compared to placebo and native **Hyaluronan treatment**.

In addition an unexpectedly high percentage of eosinophils was found in the synovial fluid and in the **synovial membrane** of slightly **inflamed** joints **treated** with crosslinked HA. CONCLUSION: The data obtained after repeated intra-**articular** injections in normal rabbit knee joints confirm the safety profile of native **Hyaluronan**.

L22 ANSWER 7 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2001653984 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11696432
TITLE: Anti-**inflammatory** and chondroprotective effect of TSG-6 (tumor necrosis factor-alpha-stimulated gene-6) in murine models of experimental **arthritis**.
COMMENT: Erratum in: Am J Pathol 2002 Mar;160(3):1193
AUTHOR: Bardos T; Kamath R V; Mikecz K; Glant T T
CORPORATE SOURCE: Department of Orthopedic Surgery, Section of Biochemistry and Molecular Biology, Rush University, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois 60612, USA.
CONTRACT NUMBER: AR40310 (NIAMS)
AR45652 (NIAMS)
AR47135 (NIAMS)
SOURCE: American journal of pathology, (2001 Nov) 159 (5) 1711-21. Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011115
Last Updated on STN: 20020404
Entered Medline: 20011207

AB Tumor necrosis factor-alpha (TNF-alpha)-stimulated gene-6 (TSG-6) is up-regulated by various cytokines and growth factors. TSG-6 binds to **hyaluronan** in **inflamed** synovial tissue and forms a complex with a serine protease inter-alpha-trypsin inhibitor (IalphaI), increasing the protease inhibitory effect of IalphaI >100-fold. The TSG-6/IalphaI complex then blocks serine proteases, including the plasminogen-plasmin activation, probably the most important component in the activation processes of matrix metalloproteinases. To gain insight into the mechanisms of TSG-6 action in **arthritis**, we have used an autoimmune murine model (proteoglycan-induced **arthritis**) for systemic, and a **monoarticular** form of **arthritis** (antigen-induced **arthritis**) for local **treatment** of **arthritis** with recombinant mouse TSG-6 (rmTSG-6). **Intravenous** injection of rmTSG-6 induced a dramatic reduction of edema in acutely **inflamed** joints by immobilizing CD44-bound **hyaluronan** and, in long-term **treatment**, protected cartilage from degradation and blocked subchondral and periosteal bone erosion in **inflamed** joints. The intra-**articular** injection of a single dose (100 microg) of rmTSG-6 exhibited a strong chondroprotective effect for up to 5 to 7 days, **preventing** cartilage proteoglycan from metalloproteinase-induced degradation. In contrast, rmTSG-6 did not postpone the onset, nor reduce the incidence of **arthritis**. We were unable to detect any significant differences between control and rmTSG-6-**treated** animals when various serum markers (including pro- and anti-**inflammatory** cytokines, auto- and heteroantibody productions) or antigen-specific T-cell responses were compared, nor when the expressions of numerous cell surface receptors or adhesion molecules were measured. TSG-6 seems to play a critical negative

regulatory feed-back function in **inflammation**, especially in arthritic processes.

L22 ANSWER 8 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2001477554 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11520164
TITLE: Guidance by ultrasound of intra-**articular** injections in the knee and hip joints.
COMMENT: Comment in: Osteoarthritis Cartilage. 2001 Aug;9(6):509-11. PubMed ID: 11520163
AUTHOR: Qvistgaard E; Kristoffersen H; Terslev L; Danneskiold-Samsoe B; Torp-Pedersen S; Bliddal H
CORPORATE SOURCE: The Parker Institute, Department of Rheumatology, H:S Frederiksberg Hospital, Copenhagen, Denmark.
SOURCE: Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society, (2001 Aug) 9 (6) 512-7. Journal code: 9305697. ISSN: 1063-4584.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010827
Last Updated on STN: 20011008
Entered Medline: 20011004

AB OBJECTIVE: To develop and assess a stable **method** for ascertaining the placement of **intraarticular** injections for **osteoarthritis** (OA) in the hip and knee. **METHODS:** Injections into the hip or knee joint with e.g. **hyaluronan** or cortisone were performed under the guidance of ultrasound. For this purpose an Acuson Sequoia apparatus and a 8-15 MHz transducer were used. After perforation of the capsule with a 21 G needle, 0.5-1 ml of atmospheric air and 1 ml lidocain 1% was injected with simultaneous recording of the ultrasound signals. This **procedure** was undertaken before the injection of the medication through the in situ needle. RESULTS: In the hip joint the injected air could readily ascertain the placement of the injection with a sharp echoic contrast forming on the ultrasound picture respecting the joint cavity. In the knee joint the **procedure** gave the best results in joints which have a small amount of fluid in either the suprapatellar bursa or in a pouch regularly observed over the lateral joint margin. However, also in some so-called 'dry' knee joints the air could be traced in the bursa by ultrasound. CONCLUSION: By the injection of air, it is possible to test the placement of **intraarticular** injections in both hip and knee joints. This **procedure** will give a supplementary documentation of the injection as compared to a mere ultrasonographic demonstration of the position of the needle in the joint. The **method** is proposed as a tool for both learning purposes and quality assurance in daily **therapy**.

L22 ANSWER 9 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2001237407 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11302324
TITLE: The increasing need for nonoperative **treatment** of patients with **osteoarthritis**.
AUTHOR: Buckwalter J A; Stanish W D; Rosier R N; Schenck R C Jr; Dennis D A; Coutts R D
CORPORATE SOURCE: University of Iowa Department of Orthopaedics, Iowa City 52242, USA.

SOURCE: Clinical orthopaedics and related research, (2001 Apr) (385) 36-45. Ref: 91
Journal code: 0075674. ISSN: 0009-921X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010503

AB **Osteoarthritis** affects more patients than almost any other musculoskeletal disorder. The number of patients suffering joint pain and stiffness as a result of this disease will increase rapidly in the next decade. Although operative **treatments** of patients with **osteoarthritis** will continue to improve and the number of operative **procedures** will increase slightly in the next decade, only a small fraction of the patients with **osteoarthritis** will require operative **procedures**. The most pressing healthcare need for the majority of patients with **osteoarthritis** is nonoperative care that helps relieve symptoms and improve function, and in some instances slows progression. In rare instances, the symptoms of **osteoarthritis** improve spontaneously, but most patients need nonoperative care for decades. Orthopaedists need to improve their ability to provide nonoperative care for patients with **osteoarthritis**. They should be skilled in the early diagnosis of **osteoarthritis** and in the use of current common nonoperative **treatments** including patient education, activity modification, shoe modifications, braces, oral analgesics, oral nonsteroidal antiinflammatory medications, oral dietary supplements, and **intraarticular** injections. Furthermore, orthopaedists should be prepared to incorporate new nonoperative **treatments** for patients with **osteoarthritis** into their practice.

L22 ANSWER 10 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2000513075 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11071576
TITLE: Role of intra-**articular** hyaluronic acid preparations in medical management of **osteoarthritis** of the knee.
AUTHOR: Hochberg M C
CORPORATE SOURCE: Division of Rheumatology and Clinical Immunology, University of Maryland School of Medicine, Veterans Affairs Maryland Health Care System at Baltimore, USA.
SOURCE: Seminars in arthritis and rheumatism, (2000 Oct) 30 (2 Suppl 1) 2-10. Ref: 40
Journal code: 1306053. ISSN: 0049-0172.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010215

AB OBJECTIVE: This article reviews the various pharmacological modalities for

the **treatment** of **osteoarthritis** (OA) of the knee, with a **particular** emphasis on the use of intra-**articular** (**IA**) hyaluronic acid (HA). **METHODS**: A literature review of the pharmacotherapy of OA of the knee was performed. Reviewed studies included those involving acetaminophen, nonsteroidal anti-**inflammatory** drugs (NSAIDs), topical analgesics, **IA** corticosteroids, and **IA** HA. RESULTS: According to American College of Rheumatology (ACR) guidelines, acetaminophen should be used as first-line oral **therapy**. NSAIDs can be tried if nonpharmacological **therapy** and acetaminophen fail to provide adequate symptom relief. Topical capsaicin cream, either as monotherapy or as adjunctive **therapy**, is recommended for patients who do not respond to analgesics or who do not wish to take systemic **therapy** . **IA** corticosteroids are recommended for patients who have an effusion and local signs of **inflammation**. **IA** HA preparations are indicated for the **treatment** of pain in patients with OA of the knee who have failed to respond adequately to conservative nonpharmacologic **therapy** and to simple analgesics. Clinical trials show that **IA** HA **therapy** results in improvement in knee pain and function that is superior to placebo and comparable to NSAIDs. CONCLUSIONS: **Treatment** with **IA** HA products appears to offer a significant advantage over aspiration and placebo injections for up to 6 months. It also may have an advantage over **IA** glucocorticoids.

L22 ANSWER 11 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2000397431 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10937628
TITLE: Amelioration of disease severity by **intraarticular** hylan **therapy** in bilateral canine **osteoarthritis**.
AUTHOR: Mârshall K W; Manolopoulos V; Mancer K; Staples J; Damyanovich A
CORPORATE SOURCE: Division of Orthopaedics, The Toronto Hospital Arthritis Centre, Ontario, Canada.. kwm@uhnres.utoronto.ca
SOURCE: Journal of orthopaedic research : official publication of the Orthopaedic Research Society, (2000 May) 18 (3) 416-25. Journal code: 8404726. ISSN: 0736-0266.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000824
Last Updated on STN: 20000824
Entered Medline: 20000817

AB Because of its high molecular weight, the glycosaminoglycan molecule **hyaluronan** is responsible for the viscoelastic properties of normal synovial fluid. In **osteoarthritis**, the concentration and molecular weight of **hyaluronan** in synovial fluid is diminished: this impairs the ability of synovial fluid to effectively lubricate joints, absorb loads, and exert anti-**inflammatory** effects. Using a bilateral anterior cruciate-ligament transection and partial neurectomy canine model of **osteoarthritis**, this study examined the effect of viscosupplementation with hylan G-F 20 as a **treatment** for **osteoarthritis**. Twelve dogs underwent bilateral arthroscopic anterior cruciate-ligament transections and partial neurectomy of the knee joints. Beginning 1 week after the operation, six dogs received three weekly 500-microl injections of hylan G-F 20 in one knee and a sham injection of saline solution in the contralateral knee

(early-**treatment** group). The remaining six animals underwent the same **treatment** 2 months following the **procedure** (late-**treatment** group). All dogs were killed at 8 months, and both knees were evaluated for gross pathology, histology, and proteoglycan content. In addition, with use of 500-MHz [1H] magnetic resonance spectroscopy, the synovial fluid from both knees was assessed for changes in metabolic profile. Differences in outcome were analyzed with paired t tests. Gross pathological and histological examination revealed significantly less severe changes of **osteoarthritis** in knees **treated** with hylan G-F 20 2 months after surgery than in the contralateral untreated knees. Magnetic resonance spectroscopy of the specimens in this late-**treatment** group showed significantly decreased glucose concentrations and significantly elevated isoleucine levels in the synovial fluid from knees **treated** with hylan G-F 20 compared with the controls. Previous magnetic resonance spectroscopy had shown that glucose concentrations increase with the onset of **osteoarthritis** and eventually diminish in end-stage **osteoarthritis**. The three injections of hylan were given after **osteoarthritis** was established, and the severity of the disease was ameliorated in the **treated** knees 6 months after **treatment**. This occurred although hylan G-F 20 is almost certainly cleared from joints by lymphatics within 4 weeks of injection, suggesting that hylan **therapy** can retard the progression of **osteoarthritis** for periods of time extending beyond the **intraarticular** residence time of the injected molecules and that hylan injections given at relatively early stages of **osteoarthritis** may have a chondroprotective effect. No changes in outcome were noted in the animals that received hylan G-F 20 immediately following surgery.

L22 ANSWER 12 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2000242923 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10782829
TITLE: Hyaluronic acid inhibits the expression of u-PA, PAI-1, and u-PAR in human synovial fibroblasts of **osteoarthritis** and rheumatoid **arthritis**.
AUTHOR: Nonaka T; Kikuchi H; Ikeda T; Okamoto Y; Hamanishi C; Tanaka S
CORPORATE SOURCE: Department of Orthopaedic Surgery, Kinki University School of Medicine, Osakasayama, Japan.
SOURCE: Journal of rheumatology, (2000 Apr) 27 (4) 997-1004. Journal code: 7501984. ISSN: 0315-162X.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000621

AB OBJECTIVE: **Intraarticular** administration of hyaluronic acid (HA) has been widely used for the **treatment** of **osteoarthritis** (OA). Fibrinolysis is closely related to the pericellular proteolysis involved in **inflammation**. However, the role of HA in the regulation of fibrinolytic factors is not yet known. We investigated the effect of HA on the pericellular fibrinolytic system of human synovial fibroblasts derived from OA and rheumatoid **arthritis** (RA). **METHODS**: Human synovial fibroblasts obtained from OA and RA were cultured in the presence and absence of HA. The antigen of urokinase-type plasminogen activator (u-PA) and plasminogen activator inhibitor-1 (PAI-1)

were measured by ELISA, and u-PA activity was evaluated by electrophoretic enzymography. The binding assay of u-PA and the immunohistochemical analysis of u-PA were employed to detect u-PA receptor (u-PAR). RESULTS: HA suppressed the secretion of both u-PA and PAI-1 antigens from the synovial fibroblasts of OA to their conditioned medium. Suppression of u-PA activity in OA synovial fibroblasts was more marked than in those of RA. The u-PA binding assay of OA and RA synovial fibroblasts revealed a single class of binding site: dissociation constant (Kd) 23.7 nM, maximal number of binding sites (Bmax) 3.11x10(4) binding sites/cell; Kd 16.5 nM, Bmax of 9.88x10(4) binding sites/cell, respectively. HA decreased Bmax in fibroblasts of both OA and RA. Immunohistochemical analysis showed that u-PAR was constitutively expressed in both synovial fibroblasts, but if these cells were **treated** with HA, the decrease of the staining of u-PAR was more pronounced in the cells of RA than in OA. CONCLUSION: Pericellular fibrinolytic activity mediated by the u-PA/u-PAR system and PAI-1 was attenuated by HA in synovial fibroblasts derived from OA and RA. Thus, HA may be a useful agent to inhibit the **inflammation** of **arthritis**.

L22 ANSWER 13 OF 49 MEDLINE on STN
ACCESSION NUMBER: 1999171508 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10073500
TITLE: The pathobiology of **osteoarthritis** and the rationale for the use of pentosan polysulfate for its **treatment**.
AUTHOR: Ghosh P
CORPORATE SOURCE: Department of Surgery, University of Sydney, The Institute of Bone and Joint Research, Royal North Shore Hospital of Sydney, St Leonards, NSW, Australia.. pghosh@mail.usid.edu.au
SOURCE: Seminars in arthritis and rheumatism, (1999 Feb) 28 (4) 211-67. Ref: 390
Journal code: 1306053. ISSN: 0049-0172.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 19990511
Entered Medline: 19990429

AB OBJECTIVES: Structure-modifying **osteoarthritis** (OA) drugs (SMOADs) may be defined as agents that reverse, retard, or stabilize the underlying pathology of OA, thereby providing symptomatic relief in the long-term. The objective of this review was to evaluate the literature on sodium pentosan polysulfate (NaPPS) and calcium pentosan polysulfate (CaPPS), with respect to the pathobiology of OA to ascertain whether these agents should be classified as SMOADs. **METHODS**: Published studies on NaPPS and CaPPS were selected on the basis of their relevance to the known pathobiology of OA, which also was reviewed. RESULTS: Both NaPPS and CaPPS exhibit a wide range of pharmacological activities. Of significance was the ability of these agents to support chondrocyte anabolic activities and attenuate catabolic events responsible for loss of components of the cartilage extracellular matrix in OA joints. Although some of the anti-catabolic activities may be mediated through direct enzyme inhibition, NaPPS and CaPPS also have been shown to enter chondrocytes and bind to promoter proteins and alter gene expression of matrix metalloproteinases and possibly other mediators. In rat models of

arthritis, NaPPS and CaPPS reduced joint swelling and **inflammatory** mediator levels in pouch fluids. Moreover, synoviocyte biosynthesis of high-molecular-weight **hyaluronan**, which is diminished in OA, was normalized when these cells were incubated with NaPPS and CaPPS or after **intraarticular** injection of NaPPS into arthritic joints. In rabbit, canine, and ovine models of OA, NaPPS and CaPPS preserved cartilage integrity, proteoglycan synthesis, and reduced matrix metalloproteinase activity. NaPPS and CaPPS stimulated the release of tissue plasminogen activator (t-PA), superoxide dismutase, and lipases from vascular endothelium while concomitantly decreasing plasma levels of the endogenous plasminogen activator inhibitor PAI-1. The net thrombolytic and lipolytic effects exhibited by NaPPS and CaPPS may serve to improve blood flow through subchondral capillaries of OA joints and improve bone cell nutrition. In geriatric OA dogs, NaPPS and CaPPS reduced symptoms, as well as normalized their thrombolytic status, threshold for platelet activation, and plasma triglyceride levels. These hematologic parameters were shown to be abnormal in OA animals before drug **treatment**. Similar outcomes were observed in OA patients when CaPPS or NaPPS were given orally or parenterally in both open and double-blind trials. CONCLUSIONS: The data presented in this review support the contention that NaPPS and CaPPS should be classified as SMOADs. However, additional long-term clinical studies employing **methods** of assessing joint structural changes will be needed to confirm this view.

L22 ANSWER 14 OF 49 MEDLINE on STN
ACCESSION NUMBER: 1999086422 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9870875
TITLE: Gelatin/chondroitin 6-sulfate microspheres for the delivery of **therapeutic** proteins to the joint.
AUTHOR: Brown K E; Leong K; Huang C H; Dalal R; Green G D; Haimes H B; Jimenez P A; Bathon J
CORPORATE SOURCE: University of Maryland, College Park, USA.
CONTRACT NUMBER: CA-68011 (NCI)
SOURCE: Arthritis and rheumatism, (1998 Dec) 41 (12) 2185-95. Journal code: 0370605. ISSN: 0004-3591.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990216
Last Updated on STN: 20000303
Entered Medline: 19990201

AB OBJECTIVE: To develop a biodegradable, **inflammation**-responsive microsphere system for the **intraarticular** delivery of **therapeutic** proteins. **METHODS**: Microspheres were synthesized by complex coacervation. Radiolabeled protein release and microsphere degradation were assessed by exposing the microspheres to human synovial fluids (SF) and recombinant gelatinase. Microsphere degradation was confirmed by scanning electron microscopy (SEM). Microsphere biocompatibility was evaluated in vitro by incubating the microspheres with human synoviocytes, and in vivo by injection into mouse joints. RESULTS: Optimal microsphere formulation was developed. Significant (up to 100%) release of encapsulated protein occurred in SF samples with measurable metalloprotease activity, while release was minimal in SF with negligible activity. Dissolution of microspheres exposed to gelatinase was confirmed by SEM. Microspheres were found to be noncytotoxic in vitro, and noninflammatory in vivo. CONCLUSION: Microsphere encapsulation is an **inflammation**-responsive and

biocompatible system of protein delivery that holds promise for use in the delivery of **therapeutic** proteins to the joint.

L22 ANSWER 15 OF 49 MEDLINE on STN
ACCESSION NUMBER: 97470776 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9331236
TITLE: The effect of hyaluronic acid on experimental temporomandibular joint osteoarthrosis in the sheep.
AUTHOR: Neo H; Ishimaru J I; Kurita K; Goss A N
CORPORATE SOURCE: Oral and Maxillofacial Surgery Unit, The University of Adelaide, South Australia.
SOURCE: Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons, (1997 Oct) 55 (10) 1114-9.
Journal code: 8206428. ISSN: 0278-2391.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Dental Journals; Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971030

AB PURPOSE: The purpose of this study was to test the effect of repeated injections of hyaluronic acid (HA) on the sheep model of osteoarthrotic temporomandibular joint (TMJ) disease. MATERIALS AND **METHODS**: Bilateral osteoarthrosis (OA) was induced in the TMJs of six sheep. HA was injected into one joint on 7, 10, 14, 17, and 21 days postoperatively. Normal saline was injected into the contralateral joint. Three sheep were killed at 1 month and 3 at 3 months. The joints were removed and examined macroscopically and histologically. A special scoring system was applied following the modified Mankin's score to evaluate the histologic changes. RESULTS: The control group showed severe osteoarthrotic changes in the condyle, deviation in form from normal morphology, and marked marrow fibrosis. The HA-**treated** group showed less deviation from normal condylar morphology. The histologic scores at 1 month were HA 12.6, control 24.2 ($P < .001$), and at 3 months were HA 6.9, control 18.9 ($P < .001$). There was a significant difference in osteoarthrotic changes between HA-**treated** and control TMJs, with the HA-**treated** TMJs having less severe changes. CONCLUSION: Repeated **intraarticular** injections of HA into a sheep TMJ with experimentally induced OA minimizes the extent of osteoarthrotic change when compared with the control joint. Thus, HA may have a role in **preventing** the progression of TMJ OA.

L22 ANSWER 16 OF 49 MEDLINE on STN
ACCESSION NUMBER: 97469195 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9328667
TITLE: Effects of **intravenous** administration of sodium hyaluronate on carpal joints in exercising horses after arthroscopic surgery and osteochondral fragmentation.
AUTHOR: Kawcak C E; Frisbie D D; Trotter G W; McIlwraith C W; Gillette S M; Powers B E; Walton R M
CORPORATE SOURCE: Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins 80523, USA.
SOURCE: American journal of veterinary research, (1997 Oct) 58 (10) 1132-40.
Journal code: 0375011. ISSN: 0002-9645.

PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980122
Last Updated on STN: 19980122
Entered Medline: 19971231

AB OBJECTIVE: To evaluate the effects of arthroscopic surgery, osteochondral fragmentation, and **treatment** with **IV** administered hyaluronate on histologic, histochemical, and biochemical measurements within the carpal joints of horses. ANIMALS: 12 clinically normal horses, 2 to 7 years of age. **PROCEDURE**: Horses had an osteochondral fragment created at the distal aspect of the radiocarpal bone of 1 randomly chosen middle carpal joint to simulate osteochondral fragmentation. Horses were **treated** with 40 mg of hyaluronate or saline solution (placebo) **intravenously** once a week for 3 consecutive weeks (days 13, 20, and 27 after surgery). Treadmill exercise proceeded 5 days per week beginning 15 days, and ending 72 days, after surgery. Clinical evaluations were performed at the beginning and end of the study. Synovial fluid samples were obtained aseptically from both middle carpal joints on days 0, 13, 20, 27, 34, and 72 after surgery, and total protein, **inflammatory** cell, hyaluronate, glycosaminoglycan, and prostaglandin E2 concentrations were measured in each sample. All horses were euthanatized on day 72. **Synovial membrane** and **articular** cartilage were obtained for histologic evaluation. **Articular** cartilage samples were also obtained aseptically for determining glycosaminoglycan content and chondrocyte synthetic rate for glycosaminoglycans. RESULTS: Horses **treated** with hyaluronate **intravenously** had lower lameness scores (were less lame), significantly better **synovial membrane** histologic scores, and significantly lower concentrations of total protein and prostaglandin E2 within synovial fluid 72 days after surgery, compared with placebo-**treated** horses. **Treatment** with **intravenously** administered hyaluronate had no significant effects on glycosaminoglycan content, synthetic rate or morphologic scoring in **articular** cartilage, or other synovial fluid measurements. CONCLUSION: **Intravenously** administered hyaluronate appears to alleviate signs of lameness by interacting with synoviocytes, and by decreasing production and release of **inflammatory** mediators.

L22 ANSWER 17 OF 49 MEDLINE on STN
ACCESSION NUMBER: 97451084 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9306060
TITLE: Effects of triamcinolone acetonide on an in vivo equine osteochondral fragment exercise model.
COMMENT: Comment in: Equine Vet J. 1997 Sep;29(5):331-2. PubMed ID: 9306056
AUTHOR: Frisbie D D; Kawcak C E; Trotter G W; Powers B E; Walton R M; McIlwraith C W
CORPORATE SOURCE: Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins 80523, USA.
SOURCE: Equine veterinary journal, (1997 Sep) 29 (5) 349-59. Journal code: 0173320. ISSN: 0425-1644.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971106

AB The objective of this study was to determine the effects of intra-**articularly** administered triamcinolone acetonide (TA) in exercised equine athletes with carpal osteochondral fragmentation. Eighteen horses were randomly assigned to each of 3 groups. An osteochondral chip fragment was created in one randomly chosen intercarpal joint of each horse. Both intercarpal joints in the placebo control group (CNT) horses were injected with intra-**articular** administration (**IA**) of polyionic fluid. Both joints in the TA control group (TA CNT) horses were **treated** with 12 mg of TA in the intercarpal joint without an osteochondral fragment, and the opposite intercarpal joint was injected with a similar volume of polyionic fluid. The TA **treated** group (TA TX) horses were **treated** with 12 mg of TA in the joint that contained the osteochondral fragment and the opposite intercarpal joint was injected with a similar volume of polyionic fluid. All horses were **treated IA** on days 13 and 27 after surgery and exercised on a high speed treadmill for 6 weeks starting on Day 14. Horses in the TA TX group were significantly less lame than horses in the CNT and TA CNT groups. Horses in either TA CNT or TA TX groups had lower total protein, and higher **hyaluronan**, and glycosaminoglycan concentrations in synovial fluid than did those in the CNT group. **Synovial membrane** collected from subjects in TA CNT and TA TX groups had significantly less **inflammatory** cell infiltration, subintimal hyperplasia and subintimal fibrosis compared to the CNT group. **Articular** cartilage histomorphological parameters were significantly better from the TA CNT and TA TX groups compared to the CNT group. In conclusions, results from this study support favourable effects of TA on degree of clinically detectable lameness, and on synovial fluid, **synovial membrane**, and **articular** cartilage morphological parameters, both with direct intra-**articular** administration and remote site administration as compared to placebo **treatment**. The clinical use of **IA** administered TA in horses may be **therapeutically** beneficial in selected cases of osteochondral fragmentation and **osteoarthritis**.

L22 ANSWER 18 OF 49 MEDLINE on STN
ACCESSION NUMBER: 96057288 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7562764
TITLE: Acute local reactions after **intraarticular** hylan for **osteoarthritis** of the knee.
COMMENT: Comment in: J Rheumatol. 1996 May;23(5):944-5; author reply 946. PubMed ID: 8724316
Comment in: J Rheumatol. 1996 May;23(5):945-6. PubMed ID: 8724318
AUTHOR: Puttick M P; Wade J P; Chalmers A; Connell D G; Rangno K K
CORPORATE SOURCE: Department of Medicine, University of British Columbia, Vancouver, Canada.
SOURCE: Journal of rheumatology, (1995 Jul) 22 (7) 1311-4.
Journal code: 7501984. ISSN: 0315-162X.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19980206
Entered Medline: 19951122

AB OBJECTIVE. To describe acute local reactions following **intraarticular** hylan injection and determine their frequency. **METHODS**. Retrospective review of all patients with **osteoarthritis** of the knee **treated** with hylan by 3 rheumatologists. RESULTS. Twenty-two patients had 88 injections to 28 knees. Six patients had reactions within 24 h of injection characterized by pain, warmth, and swelling, lasting up to 3 weeks. This occurrence was unpredictable. Corticosteroid injections were sometimes required. Synovial fluid cell counts were 5.0-75.0 x 10(9)/l, often with a prominent mononuclear component. Crystal studies and cultures were negative. Radiographic chondrocalcinosis was present in only 1 patient. One patient had serum antibodies to chicken serum proteins. CONCLUSION. **Intraarticular** hylan was associated with significant local **inflammatory** reactions in 27% of patients, or 11% of injections. The mechanism(s) and long term sequelae are unclear.

L22 ANSWER 19 OF 49 MEDLINE on STN
ACCESSION NUMBER: 95031326 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7944639
TITLE: Intra-**articular** injections of 750 kD **hyaluronan** in the **treatment** of **osteoarthritis**: a randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy.
AUTHOR: Henderson E B; Smith E C; Pegley F; Blake D R
CORPORATE SOURCE: Inflammation Group, Clinical Studies Division, Royal London Hospital Medical College, United Kingdom.
SOURCE: Annals of the rheumatic diseases, (1994 Aug) 53 (8) 529-34. Journal code: 0372355. ISSN: 0003-4967.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19941222
Entered Medline: 19941031

AB OBJECTIVE--To determine the safety and efficacy of intra-**articular** injections of **hyaluronan** in the **treatment** of **osteoarthritis** of the knee. **METHODS**--A randomised double-blind placebo-controlled trial was carried out on 91 patients with radiologically confirmed **osteoarthritis** of the knee who were recruited from the outpatient clinics. RESULTS--It was found that weekly **intraarticular** injections of 20 mg of **hyaluronan** of M(r) = 750,000 (Hyalgan) in 2 ml of buffered saline performed no better than the inert vehicle alone over a five week period. The principal side effects of a transient increase in pain and swelling in the affected knee was observed in 47% of the **treatment** group compared with 22% of the placebo group. A few patients with radiologically mild disease **treated** with Hyalgan appeared to experience medium to long-term symptomatic improvement over matched placebo controls as judged by a delayed return to previous NSAID **therapy** or analgesia other than paracetamol. Patient numbers in the survival groups, however, were too small to be meaningful. CONCLUSION--It is concluded that

intraarticular administration of this preparation of 750 kD **hyaluronan** offers no significant benefit over placebo during a five week **treatment** period, but incurs a significantly higher morbidity, and therefore has no place in the routine **treatment** of **osteoarthritis**.

L22 ANSWER 20 OF 49 MEDLINE on STN
ACCESSION NUMBER: 94175933 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7510481
TITLE: The effects of orally administered calcium pentosan polysulfate on **inflammation** and cartilage degradation produced in rabbit joints by **intraarticular** injection of a hyaluronate-polylysine complex.
AUTHOR: Smith M M; Ghosh P; Numata Y; Bansal M K
CORPORATE SOURCE: Raymond Purves Bone and Joint Research Laboratories, (University of Sydney), Royal North Shore Hospital, Australia.
SOURCE: Arthritis and rheumatism, (1994 Jan) 37 (1) 125-36. Journal code: 0370605. ISSN: 0004-3591.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940420
Last Updated on STN: 19960129
Entered Medline: 19940408

AB OBJECTIVE. To determine the antiinflammatory and cartilage-protecting activities of orally administered calcium pentosan polysulfate (CaPPS) in a rabbit model of **inflammatory arthritis**.
METHODS. A single **intraarticular** injection of a preformed polycation complex (PC) of poly-D-lysine and **hyaluronan** was used to induce joint **inflammation**; saline was injected into the contralateral joint as a control. Animals were killed 1, 4, 7, or 10 days post-PC injection. CaPPS, at 5 mg/kg, 10 mg/kg, or 75 mg/kg, was given every 48 hours commencing 7 days prior to PC injection. Serum interleukin-6 (IL-6), synovial fluid (SF) prostaglandin E2, cell numbers, and cartilage proteoglycan (PG) content, composition, and biosynthesis were determined for PC- and saline-injected joints. RESULTS. In PC-injected, non-drug-**treated** animals, serum IL-6 activity, SF leukocyte numbers, and prostaglandin E2 levels were elevated, while cartilage PG content and biosynthesis were reduced. CaPPS at 10 mg/kg, but not at 5 mg/kg, decreased serum IL-6 levels but maintained cartilage PG concentration and biosynthesis. However, SF leukocyte counts and prostaglandin E2 levels (except on day 1) were not reduced. CONCLUSION. The ability of CaPPS to attenuate serum IL-6 levels and preserve cartilage PGs in **inflamed** rabbit joints suggests that this substance could be of value as an effective orally administered chondroprotective, antiarthritic drug.

L22 ANSWER 21 OF 49 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:379226 BIOSIS
DOCUMENT NUMBER: PREV200100379226
TITLE: **Hyaluronan** suppressed nitric oxide production in the meniscus and synovium of rabbit **osteoarthritis** model.
AUTHOR(S): Takahashi, Kenji; Hashimoto, Sanshiro; Kubo, Toshikazu; Hirasawa, Yasusuke; Lotz, Martin; Amiel, David [Reprint author]

CORPORATE SOURCE: Department of Orthopedics, School of Medicine, University of California, San Diego, 9500 Gilman Drive, Dept 0630, La Jolla, CA, 92093-0630, USA
damiel@ucsd.edu
SOURCE: Journal of Orthopaedic Research, (May, 2001) Vol. 19, No. 3, pp. 500-503. print.
CODEN: JOREDR. ISSN: 0736-0266.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Aug 2001
Last Updated on STN: 19 Feb 2002

AB Nitric oxide (NO) plays an important role in cartilage degeneration, and NO donors induce meniscus degeneration and synovium **inflammation**. This study evaluated the effect of **intraarticular** injections of **hyaluronan** (HA) on NO production in meniscus and synovium using an experimental **osteoarthritis** (OA) model. Thirty-six New Zealand white rabbits underwent unilateral anterior cruciate ligament transection (ACLT), and were divided into three groups. Four weeks after ACLT, the HA group started to receive **intraarticular** HA injections once a week for 5 weeks; the vehicle group started to receive the carrier of HA; and the no injection group, no **treatment**. All ACLT knees were harvested at the 9th week. Meniscus and synovium sections were examined by immunohistochemistry for nitrotyrosine. The pieces of these two tissues were cultured for 24 h. Culture supernatants were analyzed for nitrite concentration. The amount of NO produced by the meniscus was much larger than that produced by the synovium. NO productions in the meniscus and synovium of the HA group were significantly lower than those of the other groups. The results suggest that the inhibition of NO production in meniscus and synovium might be a part of the mechanism of the **therapeutic** effect of HA on OA.

L22 ANSWER 22 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004077516 EMBASE
TITLE: [Viscosupplementation in the **treatment** of **osteoarthritis**].
WISKOSUPLEMENTACJA W LECZENIU CHOROBY ZWYRODNIENIOWEJ STAWOW.
AUTHOR: Filipowicz-Sosnowska A.; Stanislawsyka-Biernat E.; Kwiatkowska B.
CORPORATE SOURCE: A. Filipowicz-Sosnowska, Klinika Reumatologii IR, Warszawa, Poland
SOURCE: Reumatologia, (2003) 41/4 (425-435).
Refs: 22
ISSN: 0034-6233 CODEN: RMTOA2
COUNTRY: Poland
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: Polish
SUMMARY LANGUAGE: English; Polish

AB **Osteoarthritis** is the most frequent pathology of musculo-skeletal system in which all elements of joint are involved: cartilage, subchondral bone, **synovial membrane** and synovial fluid. Hialuronic acid is a main component of synovial fluid. Hialuroniane is a glicosaminoglican, syntetised by synoviocytes and released to the synovial fluid. The joint viscoelascity and joint homeostasis are strictly dependent on hialuronians properties. In **osteoarthritis**, molecular weight of hialuronians as well as its

concentration is significantly diminished. Viscosupplementation is the **treatment** options in **osteoarthritis** of the knee and it is based on aspiration of the pathological synovial fluid and its supplementation by hialuronians. In the several clinical studies it has been shown that viscosupplementation improves the biomechanical properties of the joint, acts as symptom modyfing (improvement in pain assessment and joint function) and cartilage structure modyfing **method**. The improvement in pain assessment and anti-**inflammatory** effects of hialuronians is comparable to nonsteroid anti-**inflammatory** drugs (NSAID). In the studies based on experimental models it has been documented that hialuronians induces the proteoglican synthesis by chondrocytes, diminished metalloproteinase (MMP-3) production and inhibits the realese of **inflammatory** mediators (cytokines and prostaglandines). The use of viscosupplementation in the **treatment** of knee **osteoarthritis** is recommended, by some authors, especially in patients who do not respond to non-pharmacological **treatment** and paracetamol with contraindications to NSAIDs and coxibs.

L22 ANSWER 23 OF 49 EMBASE
on STN

ACCESSION NUMBER: 2004051311 EMBASE
TITLE: The Young Adult with Hip Pain: Diagnosis and Medical **Treatment**, Circa 2004.
AUTHOR: Troum O.M.; Crues III J.V.
CORPORATE SOURCE: Dr. O.M. Troum, 2336 Santa Monica Blvd., Santa Monica, CA 90404-2064, United States. Otroum@yahoo.com
SOURCE: Clinical Orthopaedics and Related Research, (2004) -/418 (9-17).
Refs: 51
ISSN: 0009-921X CODEN: CORTBR
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Hip pain in young adults (18-35 years old) often is characterized by nonspecific symptoms, normal imaging studies, and vague findings from the history and physical examination. In younger patients, pain is more likely to be caused by congenital hip dysplasia, athletic injuries, trauma, spondyloarthropathy, and by conditions that first appear during this stage of life, such as rheumatoid **arthritis**, **osteoarthritis**, **intravenous** drug use, alcoholism, or corticosteroid use. The history and physical examination may narrow the diagnosis to **intraarticular**, **extraarticular**, or referred sources of pain. Plain radiography and magnetic resonance imaging are the preferred initial imaging **procedures**. Analyses of the blood, urine, and synovial fluid can be helpful in diagnosing **inflammation**, infection, and systematic rheumatic disease. Fractures, infection, and ischemic necrosis should be ruled out early because they require immediate **treatment** to **prevent** damage to the joint. Hip trauma at a young age increases the risk of **osteoarthritis** with advancing age, and, unlike most older adults, young adults receiving total hip replacement can expect revision surgery. Medical **treatment** often involves patient education, physical **therapy**, and pharmacotherapy. Acetaminophen, nonsteroidal antiinflammatory drugs, and opioids for pain and antibiotics for infection are the most often prescribed drugs for this population.

L22 ANSWER 24 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004004171 EMBASE
TITLE: Letter to editor (multiple letters).
AUTHOR: Moskowitz R.; Pritchard C.H.
CORPORATE SOURCE: Prof. Dr. R. Moskowitz, Division of Rheumatology, Case Western Reserve University, Parkway Medical Center, 3609 Park East Drive, Ste 307N, Beachwood, OH 44122, United States. rwm3@po.cwru.edu
SOURCE: Journal of Musculoskeletal Research, (2003) 7/2 (v-vii+ix). ISSN: 0218-9577 CODEN: JMURFZ
COUNTRY: Singapore
DOCUMENT TYPE: Journal; Letter
FILE SEGMENT: 031 Arthritis and Rheumatism
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

L22 ANSWER 25 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003516544 EMBASE
TITLE: [Intra-**articular** injection. Substances and techniques].
DIE INTRAARTIKULARE INJEKTION. SUBSTANZEN UND TECHNIKEN.
AUTHOR: Von Stechow D.; Rittmeister M.
CORPORATE SOURCE: Dr. D. Von Stechow, Abteilung fur Rheumaorthopadie, Orthopadische Universitatsklinik, Johann-Wolfgang-Goethe-Universitat, Marienburgstrasse 2, 60528 Frankfurt am Main, Germany. d.vonstechow@friedrichsheim.de
SOURCE: Orthopade, (2003) 32/12 (1127-1135).
Refs: 65
ISSN: 0085-4530 CODEN: ORHPBG
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 033 Orthopedic Surgery
036 Health Policy, Economics and Management
037 Drug Literature Index
LANGUAGE: German
SUMMARY LANGUAGE: English; German
AB Intra-**articular** injections are widely used in the **treatment** of joint pain and/or **inflammation**. Low costs, effectiveness, and safety are offered as possible reasons. The **method** remains controversial, as the evidence supporting the efficacy of these **procedures** has been poor. To evaluate intra-**articular therapy**, a meta-analysis of the efficacy of various agents injected intra-**articularly** was performed. Furthermore, indications and medications are discussed.

L22 ANSWER 26 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003422910 EMBASE
TITLE: A cross-sectional retrospective assessment of anti-arthritic drugs in patients with **arthritis** in Korea.
AUTHOR: Lee M.C.; Lee S.; Suh D.-C.; Kim J.; Kong S.X.
CORPORATE SOURCE: Prof. S. Lee, Department of Orthopedic Surgery, Guro Hospital, Korea University, 97 Gurodonggil, Gurogu, Seoul 152-703, Korea, Republic of. leeshmd@yahoo.com

SOURCE: Current Medical Research and Opinion, (2003) 19/7 (597-602).
Refs: 20
ISSN: 0300-7995 CODEN: CMROCX
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 031 Arthritis and Rheumatism
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background: Selective cyclo-oxygenase-2 (COX-2) inhibitors were recently introduced for the **treatment** of **arthritis** because of their lower rates of gastrointestinal adverse events compared with traditional non-steroidal anti-**inflammatory** drugs (NSAIDs). Objective: To examine the medication usage patterns for both **osteoarthritis** (OA) and rheumatoid **arthritis** (RA) in Korea. **Methods**: The medical charts of a convenience sample of 402 patients with OA or RA were reviewed by the **Arthritis** Study Group in 14 hospitals and ten clinics in Korea. Results: Traditional oral NSAIDs were the most commonly prescribed drugs for OA (68.3%) and RA (65.1%) patients. Two-thirds (66.7%) of the RA patients taking COX-2 inhibitors were prescribed other **arthritis** medications concurrently and 85.1% of RA patients taking NSAIDs were prescribed other **arthritis** medications concurrently. Patients on NSAIDs were almost twice as likely to have a gastroprotective agent (GPA) concurrently compared to COX-2 inhibitor users (OA patients 38.1% vs 21.2%; RA patients 57.9% vs 30.6%). Overall, patients taking COX-2 inhibitors were less likely to take GPAs concurrently compared to patients not taking COX-2 inhibitors (unadjusted OR 0.36; adjusted OR 0.39). Conclusions: Traditional oral NSAIDs were commonly prescribed to **arthritis** patients in Korea. In this study, patients taking COX-2 inhibitors were prescribed less adjunctive **arthritis treatments** and less gastroprotective agents than traditional oral NSAID users.

L22 ANSWER 27 OF 49 EMBASE
on STN

ACCESSION NUMBER: 2003349783 EMBASE
TITLE: Development of gene-based **therapies** for cartilage repair.
AUTHOR: Palmer G.; Pascher A.; Gouze E.; Gouze J.-N.; Betz O.; Spector M.; Robbins P.D.; Evans C.H.; Ghivizzani S.C.
CORPORATE SOURCE: Dr. S.C. Ghivizzani, Center for Molecular Orthopaedics, Harvard Medical School, BLI-152, 221 Longwood Avenue, Boston, MA 02115, United States.
sghivizzani@rics.bwh.harvard.edu
SOURCE: Critical Reviews in Eukaryotic Gene Expression, (2002) 12/4 (259-273).
Refs: 134
ISSN: 1045-4403 CODEN: CRGEEJ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
033 Orthopedic Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Articular** cartilage is **particularly** vulnerable to injury and degenerative conditions, and has a limited capacity for self-repair. Although current clinical **procedures** cannot restore a normal **articular** surface, there are a growing number of proteins that may be used to augment a repair process, or protect cartilage from degeneration. Because proteins are often difficult to administer effectively, gene **therapy** approaches are being developed to provide their sustained synthesis at sites of injury or disease. To promote cartilage repair, cDNAs can be targeted to synovium, or cartilage. Gene transfer to the synovium is generally considered more suitable for chondroprotective **therapies** that rely on expression of large amounts of anti-**inflammatory** mediators. The delivery of genes to cartilage defects to promote enhanced repair can be performed by either direct administration of gene delivery vectors, or by implantation of genetically modified chondrogenic cells. Variations of these **methods** have been used to demonstrate that exogenous cDNAs encoding growth factors can be delivered locally to sites of cartilage damage where they are expressed at physiologically relevant levels. Data is beginning to emerge that suggests that delivery and expression of these genes can influence a repair response toward the synthesis of normal **articular** cartilage in vivo. This article reviews the current status of gene delivery for cartilage healing and presents some of the remaining challenges.

L22 ANSWER 28 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003293986 EMBASE
TITLE: Primary **articular** cartilage **procedures** in the middle-aged knee.
AUTHOR: Cooper M.T.; Miller M.D.
CORPORATE SOURCE: Dr. M.D. Miller, Department of Orthopaedic Surgery, University of Virginia Health System, Box 800159, Charlottesville, VA 22908, United States
SOURCE: Sports Medicine and Arthroscopy Review, (2003) 11/2 (112-121).
Refs: 123
ISSN: 1062-8592 CODEN: SMARCV
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
033 Orthopedic Surgery
035 Occupational Health and Industrial Medicine
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The **treatment** of **articular** cartilage damage in the middle-aged knee poses a difficult problem for surgeons. Such damage is common and is often the result of trauma to be knee or repetitive impact as in sports. It is well established that cartilage possesses a poor innate ability to heal. Non-surgical **treatments** such as anti-**inflammatory** medications may provide symptomatic relief, but the damage will often progress further to **osteoarthritis**. Surgical **treatment** must be aimed at repairing the **articular** surface with a durable tissue, with mechanical properties similar to native **articular** cartilage. Although arthroscopic debridement was once believed to be beneficial, recent evidence has suggested that this provides little if any long-term relief. Subchondral abrasion, drilling, and microfracture are used to recruit marrow elements in hopes of stimulating repair. Recently, **procedures** such as autologous

osteochondral transplantation and autologous chondrocyte transplantation have been used to restore the **articular** surface. When other **methods** have failed the use of total and unicompartmental knee arthroplasty are viable options, because recent long-term results have shown success even in young, active patients.

L22 ANSWER 29 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003096588 EMBASE
TITLE: Intra-**articular treatment** of **osteoarthritis** of the knee: An arthroscopic and clinical comparison between sodium hyaluronate (500-730 kDa) and methylprednisolone acetate.
AUTHOR: Frizziero L.; Pasquali Ronchetti I.
CORPORATE SOURCE: L. Frizziero, Rheumatology Unit, Department of Internal Medicine, Maggiore Hospital, Bologna, Italy. luigifrizziero@infinito.it
SOURCE: Journal of Orthopaedics and Traumatology, (2002) 3/2 (89-96).
Refs: 33
ISSN: 1590-9921 CODEN: JOTOBV
COUNTRY: Italy
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 031 Arthritis and Rheumatism
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Corticosteroids have long represented the drugs of choice for intra-**articular treatment** of **osteoarthritis** (OA), but their use has drawbacks, indicating the need for alternatives devoid of these effects. This comparative study examined the clinical efficacy and the structural effects of intra-**articular** injections of sodium hyaluronate (HA) of molecular weight (MW) 500-730 kDa (one injection weekly for 5 weeks) versus methylprednisolone acetate (MP) (one injection weekly for 3 weeks) in the **treatment** knee OA. We studied 99 patients with knee OA, primary or secondary to a traumatic event, classified according to criteria of the American College of Rheumatology. Pain assessments by VAS and arthroscopic examinations of **synovial membrane** and cartilage were performed at baseline and 180 days after the start of the **treatment**. Arthroscopic features were evaluated under blind conditions. Initially, MP showed a more immediate beneficial clinical effect in reducing pain than HA, but after 180 days the symptomatic effect of HA was more long lasting than that of MP. Arthroscopic findings at day 180, in comparison with baseline conditions, showed that both drugs were decreased **synovial membrane inflammation** but HA was superior to MP in reducing the grade and extent of cartilage damage. HA of 500-730 kDa represents a valid alternative to corticosteroids in the intra-**articular treatment** of OA with a beneficial effect on the structural alterations. This study supports previous data on a potential structure-modifying activity of HA in OA of the knee.

L22 ANSWER 30 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003023358 EMBASE
TITLE: [The **treatment** of knee **osteoarthritis** with arthroscopic debridement and **intraarticular** hyaluronic acid injections].

DIZ OSTEOARTRITININ ARTROSKOPIK DEBRIDMAN VE INTRAARTIKULER HYALURONIK ASIT ILE TEDAVISI.

AUTHOR: Elmali N.; Inan M.; Ertem K.; Esenkaya I.; Ayan I.; Karakaplan M.

SOURCE: Artroplasti Artroskopik Cerrahi, (2002) 13/3 (131-135).
Refs: 20
ISSN: 1300-0594 CODEN: AACEFT
COUNTRY: Turkey
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: Turkish
SUMMARY LANGUAGE: English; Turkish

AB Introduction: Adjunctive **therapies** such as nonsteroidal anti-**inflammatory** drugs (NSAIDs), physiotherapy and intra-**articular** steroid injections are incorporated into an arthroscopic debridement **treatment** for knee **osteoarthritis**. Additionally, intra-**articular** injections of hyaluronic acid have been shown to provide relief of pain and improved function in patients with **osteoarthritis** of the knee. In this study, we aimed to evaluate the results of arthroscopic debridement and **intraarticular** hyaluronic acid injections in patients with knee **osteoarthritis**. Materials and **Methods**: Between April 1998 and December 1999, 29 knees in 23 patients with knee **osteoarthritis** were **treated** with knee debridement followed by three **intraarticular** sodium hyaluronate (30 mg/2ml) injections weekly over a 2-week period. The mean age of patients was 53.8 (39-63). There were 14 women and 9 men. Nineteen right, 10 left knees were **treated**. Patients were evaluated with the Hospital for Special Surgery (HSS) knee score and the Knee Society (KS) clinical rating system for pain and function before **treatment**, at the end of first year and up to mean 20.3 months (12-32 months). Chondral lesions were evaluated according to Outerbridge criteria during arthroscopic examination. Results: Overall, 23 knees of 19 patients (79.3%) had a good or excellent result in 1 year and 20 knees of 17 patients (69%) had a good or excellent result in 20.3 months. In the last evaluation of the patients whom grade I-III chondral lesions were arthroscopically diagnosed clinical improvement was continuing, and the patients with grade **IV** chondral lesion showed no improvement as compared to pretreatment. Conclusion: Although arthroscopic debridement followed by **intraarticular** sodium hyaluronate injections can provide pain relief and improvement in function for short term, further well-controlled, long-term, large clinical studies are needed to compare this **treatment** to debridement or hyaluronic acid injections alone.

ACCESSION NUMBER: 2002444074 EMBASE

TITLE: A comparison of the efficacy of conservative **therapies** for obese patients with **osteoarthritis** of the knee.

AUTHOR: Toda Y.
CORPORATE SOURCE: Y. Toda, K. Toda Orthoped. Rheumatology Clin., Toyotsu-cho, Suita-city, Japan

SOURCE: Ryumachi, (2002) 42/5 (795-800).
Refs: 22
ISSN: 0300-9157 CODEN: RYMCAF
COUNTRY: Japan
DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese
AB Two hundred and five obese women with **osteoarthritis** of the knee (knee OA) were **treated** with one of the following interventions for six weeks: A nonsteroidal anti-**inflammatory** drug (NSAID) alone (Control, n=16), NSAID combined with walking (n=16), NSAID with non-weight bearing exercises (n=16), NSAID with intra-**articular** **hyaluronan** injections (NH, n=16), NSAID with supplement foods, glucosamine and condroitin (NS, n=15), traditional shoe inserts, wedged insoles (NT, n=20), NSAID with a novel insole with an elastic subtalar strapping (NN, n=25), an energy restriction diet plus the NSAID (ND, n=32), a diet combined with the NSAID and exercises (NDE, n=25), and the diet combined with the NSAID and walking (NDW, n=24). The Lequesne index was employed to obtain remission percentages, which were then compared between the ten groups. Compared with all but the NDW group, the NDE group showed a significant improvement. The NDW group also demonstrated a significant improvement, compared with all but the NDE and NN groups. The NN group showed a significant improvement compared with the control, NS and ND groups. However, for patients in the NDE and NDW groups, it was difficult to maintain body composition, even with these intervention **methods**. In this regard, the use of the insole with the elastic subtalar strapping was a simple and convenient **method** to maintain the body composition effect of the intervention **method** for knee OA patients.

L22 ANSWER 32 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002417060 EMBASE
TITLE: **Osteoarthritis IV**: Clinical **therapeutic** trials and **treatment**.
AUTHOR: Buchanan W.W.; Kean W.F.
CORPORATE SOURCE: W.F. Kean, McMaster University, 401-1 Young Street, Hamilton, Ont. L8N 1T8, Canada
SOURCE: Inflammopharmacology, (2002) 10/1-2 (79-155).
Refs: 516
ISSN: 0925-4692 CODEN: IAOAES
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB This article discusses the potential usefulness of clinical **therapeutic** trials and criticises the failure of the value of guidelines in the management of **osteoarthritis** (OA). We have provided an overview of the benefits and side effects of non steroidal anti-**inflammatory** drugs (NSAIDs) in OA, including the introduction of the COX-2 selective inhibitors. In addition we have briefly reviewed the use of local NSAIDs, narcotic analgesics, injection **methods**, disease modifying drugs, gene **therapy**, surgical **treatment**, and non pharmacological intervention.

L22 ANSWER 33 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002359737 EMBASE
TITLE: [Musculoskeletal facial pain].

MUSKULOSKELETALNI LINI BOLEST.
AUTHOR: Krug J.; Cevallos-Lecaro M.D.; Grummichova M.
CORPORATE SOURCE: Dr. J. Krug, Univerzita Karlova, Lekarska Fak., Fakultni Nemocnice, 500 05 Hradec Kralove, Czech Republic. jirikrug@hotmail.com
SOURCE: Bolest, (2002) 5/3 (146-151).
Refs: 23
ISSN: 1212-0634 CODEN: BOLECA
COUNTRY: Czech Republic
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
037 Drug Literature Index
LANGUAGE: Czech
SUMMARY LANGUAGE: Czech; English
AB Musculoskeletal pain is after odontalgia the second most common pain in head and neck region. At the same time pain is the chief complaint in most temporomandibular disorders and all muscular troubles. The principle of pain management is usage of the conservative **methods** and sequental loading of the more serious and invasive **therapy**. The most frequent painful problems in the temporomandibular joint region are protective cocontraction, local muscular tenderness, myofascial pain and dysfunction, and fibromyalgia. Most frequent painful joint disorders are capsulitis, **synovitis**, and retrodiscitis (**inflammatory** disturbance of the soft parts of temporomandibular joint), and osteoartritis. Authors describe in details some categories of painful troubles of temporomandibular joint and present the most useful way of conservative **treatment** of the artralgias. Based on clinical experiences, the **therapeutical** algorithm for the diagnostic categories is displayed.

L22 ANSWER 34 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002310198 EMBASE
TITLE: Oral and intra-**articular** remedies: Review of papers published from March 2001 to February 2002.
AUTHOR: Jubb R.W.
CORPORATE SOURCE: Dr. R.W. Jubb, University of Birmingham, Selly Oak Hospital, Raddelbarn Road, Selly Oak, Birmingham B29 6JD, United Kingdom. Ronald.jubb@uhb.nhs.uk
SOURCE: Current Opinion in Rheumatology, (2002) 14/5 (597-602).
Refs: 45
ISSN: 1040-8711 CODEN: CORHES
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 020 Gerontology and Geriatrics
031 Arthritis and Rheumatism
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB There have been considerable advances in the drug **treatments** used to **treat osteoarthritis**. The development of selective cyclo-oxygenase inhibitors (COX-II) and confirmation of their efficacy and gastrointestinal safety will reduce **treatment** morbidity in the elderly. Guidelines for safe and appropriate use of COX-II drugs are now available. The role of anti-**inflammatory** drugs in precipitating cardiorenal events has been highlighted but remains to be fully evaluated. Glucosamine, diacerein, and **hyaluronan** may all be disease-modifying drugs for **osteoarthritis** but

confirmatory studies are still needed. .COPYRGT. 2002 Lippincott Williams & Wilkins, Inc.

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ACCESSION NUMBER: 2002056026 EMBASE
TITLE: Effects of hyaluronate sodium on pain and physical functioning in **osteoarthritis** of the knee: A randomized, double-blind, placebo-controlled clinical trial.
AUTHOR: Petrella R.J.; DiSilvestro M.D.; Hildebrand C.
CORPORATE SOURCE: Dr. R.J. Petrella, Centre for Activity and Ageing, University of Western Ontario, 1490 Richmond St N, London, Ont. N6G 2M3, Canada
SOURCE: Archives of Internal Medicine, (11 Feb 2002) 162/3 (292-298).
Refs: 37
ISSN: 0003-9926 CODEN: AIMDAP
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background: Intra-**articular** hyaluronate sodium is a relatively new **therapy** for the **treatment** of **osteoarthritis** of the knee. This randomized, double-blind clinical trial was conducted at a large primary care medical center to determine the impact of hyaluronate sodium vs conventional **therapy** on measures of pain, stiffness, and disability at rest and following functionally relevant walking and stepping activities. **Methods**: A total of 120 patients (mean age, 67 years) with unilateral grades 1 to 3 medial compartment knee **osteoarthritis** were randomized to 1 of 4 **treatment** groups: group 1, 2 mL of hyaluronate sodium at a concentration of 10 mg/mL and placebo (100 mg of lactose); group 2, nonsteroidal anti-**inflammatory** drugs (NSAIDs) (75 mg of diclofenac and 200 μg of misoprostol) and hyaluronate sodium; group 3, NSAIDs and placebo (2 mL of isotonic sodium chloride solution [saline]); and group 4, placebo (lactose and saline). Intra-**articular** hyaluronate sodium or saline (2 mL) was administered once weekly over 3 weeks while NSAIDs or lactose were administered twice daily over 12 weeks. Main Outcome Measures: (1) Western Ontario McMaster Universities Index (WOMAC) global measure of pain, stiffness, and disability; (2) visual analog scale (VAS) scores for pain at rest and following functional walking and stepping activities (self-paced walking and stepping); and (3) functional performance (exercise time, heart rate, and predicted maximum oxygen uptake) at baseline and weeks 4 and 12. Results: At week 4, significant improvement in WOMAC scores for pain and disability and VAS score for resting pain was observed in groups 1 to 3 compared with baseline measures. Groups 1 and 2 showed significantly lower self-paced stepping pain, while no change was observed in group 4. At week 12, groups 1 to 3 showed significantly greater improvement in WOMAC pain subscale score and VAS score for resting pain; however, these differences did not vary from week 4. Following self-paced walking and stepping, groups 1 and 2 reported significantly less activity pain, while group 1 showed significantly faster self-paced walking and stepping test results. Groups 1 to 3 improved self-paced walking and stepping time at week 12 compared with baseline measures, while predicted maximum oxygen uptake was significantly higher in the hyaluronate sodium groups 1 and 2 at weeks 4

and 12 compared with baseline measures. Conclusions: For resting pain relief, hyaluronate sodium seems to be as effective as NSAIDs. Further, for pain with physical activity and functional performance, hyaluronate sodium may be superior to placebo alone or NSAIDs alone.

L22 ANSWER 36 OF 49 EMBASE
on STN

ACCESSION NUMBER: 2001413976 EMBASE
TITLE: The role of the rheumatologist in managing **arthritis**.
AUTHOR: Clemens L.E.
CORPORATE SOURCE: Dr. L.E. Clemens, 2 Erin Street, Richmond, Vic. 3121, Australia. lclemens@netspace.net.au
SOURCE: Medical Journal of Australia, (19 Nov 2001) 175/SUPPL. (S97-S101).
Refs: 15
ISSN: 0025-729X CODEN: MJAUAJ
COUNTRY: Australia
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 031 Arthritis and Rheumatism
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index
020 Gerontology and Geriatrics
029 Clinical Biochemistry
038 Adverse Reactions Titles
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB When and why should a patient with **arthritis** see a rheumatologist? To establish or confirm the diagnosis: aim for diagnosis within six weeks of onset. To plan an optimal management program: early, aggressive **treatment** is essential to achieve the best outcome in patients with **inflammatory arthritis**. To assess the response to **treatment**: failure to respond to **treatment** requires a change in drug regimen. Objective measures of disease activity should be used.

L22 ANSWER 37 OF 49 EMBASE
on STN

ACCESSION NUMBER: 2001264281 EMBASE
TITLE: Intra-**articular** injection of hyaluronate (SI-6601D) improves joint pain and synovial fluid prostaglandin E2 levels in rheumatoid **arthritis**: A multicenter clinical trial.
AUTHOR: Goto M.; Hanyu T.; Yoshio T.; Matsuno H.; Shimizu M.; Murata N.; Shiozawa S.; Matsubara T.; Yamana S.; Matsuda T.
CORPORATE SOURCE: Dr. M. Goto, Division of Rheumatic Diseases, Tokyo Metropolitan Otsuka Hospital, 2-8-1 Minami-Otsuka, Toshima-ku, Tokyo 170-0005, Japan. m.goto-o@ohtsuka-hospital.toshima.tokyo.jp
SOURCE: Clinical and Experimental Rheumatology, (2001) 19/4 (377-383).
Refs: 26
ISSN: 0392-856X CODEN: CERHDP
COUNTRY: Italy
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index

038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objective. The relationship between clinical features and biochemical parameters of synovial fluid after serial intra-**articular** injections of sodium hyaluronate (SI-6601D) was investigated. **Methods**. SI-6601D (sodium hyaluronate with an average molecular weight of 8.4 x 10(5); 25mg/2.5ml/syringe) was injected intra-**articularly** into the knees of 25 patients with rheumatoid **arthritis** (RA) every week for 5 consecutive weeks. Clinical and biochemical parameters were monitored before and after injection. Clinical findings included pain, as a summation of 3 categories (pain at rest, pain in motion and pain in passive motion, each assessed on a 4-step rating scale), and **inflammation**, also as a summation of 3 categories (swelling, patellar ballotement and local warmth, each assessed on a 4-step rating scale). Pain on walking of patient was qualitatively assessed by visual analogue scale (VAS). The aspirated volume of synovial fluid (SFV) was recorded and levels of prostaglandin (PG) E2, transforming growth factor beta-1, tumor necrosis factor alpha, interleukin 1 receptor antagonist, chondroitin 4-sulfate (C4S) and chondroitin 6-sulfate were measured. Results. Significant improvement in pain symptoms ($p < 0.0001$), **inflammation** ($p < 0.0001$), VAS pain ($p < 0.001$) and SFV ($p < 0.05$) were observed after the 5 injections. Levels of PGE2 ($p < 0.05$) and C4S ($p < 0.05$) in the synovial fluid were significantly decreased. Discussion. S1-6601D improved local clinical symptoms in RA patients by suppressing PGE2 and, therefore, may be a useful **treatment** for local **inflammation** in RA.

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ACCESSION NUMBER: 2001109606 EMBASE
TITLE: Morphological analysis of knee **synovial membrane** biopsies from a randomized controlled clinical study comparing the effets of sodium hyaluronate (Hyalgan ®) and methylprednisolone acetate (Depomedrol®) in **osteoarthritis**.
AUTHOR: Pasquali Ronchetti I.; Guerra D.; Taperelli F.; Boraldi F.; Bergamini G.; Mori G.; Zizzi F.; Frizziero L.
CORPORATE SOURCE: I. Pasquali Ronchetti, Department of Biomedical Sciences, University of Modena/Reggio Emilia, Via Campi 287, 41100 Modena, Italy
SOURCE: Rheumatology, (2001) 40/2 (158-169).
Refs: 46
ISSN: 1462-0324 CODEN: RUMAFK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objective. The study was part of a randomized open-label clinical trial designed to evaluate the effects of intra-**articular** injections of **hyaluronan** (Hyalgan®) (HY) in **osteoarthritis** (OA) of the human knee. Data were compared with those obtained after **treatment** with methylprednisolone acetate (Depomedrol®) (MP). **Methods. Synovial membranes** from patients with OA of the knee, primary or secondary to a traumatic event and classified according to the American College of Rheumatology criteria, were examined by arthroscopy and by light and electron microscopy before and 6 months

after local injection of HY (2 ml of 500-730 000 MW **hyaluronan**, 10 mg/ml in saline, one injection per week for 5 weeks) or MP (1 ml of methylprednisolone acetate, 40 mg/ml, one injection per week for 3 weeks). Results. Arthroscopy revealed a significant decrease in **inflammatory** score after both **treatments**. Histology showed that HY **treatment** was effective (P≤0.05) in reducing the number and aggregation of lining synoviocytes, as well as the number and calibre of the vessels. MP **treatment** significantly reduced the number of mast cells in primary OA. Both **treatments** tended to decrease the number of hypertrophic and to increase the number of fibroblast-like lining cells, to decrease the numbers of macrophages, lymphocytes, mast cells and adipocytes, and to decrease oedema, especially in primary OA, and to increase the number of fibroblasts and the amount of collagen. These phenomena were evident throughout the thickness of the synovial tissue. Conclusion. At least in the medium term, both HY and MP modified a number of structural variables of the **synovial membrane** of the osteoarthritic human knee towards the appearance of that of normal synovium. The effect was more evident in primary OA than in OA secondary to a traumatic event. This is the first evidence that local **hyaluronan** injections modify the structural organization of the human knee synovium in OA.

L22 ANSWER 39 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2000380241 EMBASE
TITLE: Sodium hyaluronate **therapy** in **osteoarthritis**: Arguments for a potential beneficial structural effect.
AUTHOR: Dougados M.
CORPORATE SOURCE: Dr. M. Dougados, Rene Descartes University, Clinique de Rhumatologie, Hopital Cochin, 27, rue du faubourg Saint Jacques, 75679 Paris, Cedex 14, France
SOURCE: Seminars in Arthritis and Rheumatism, (2000) 30/2 SUPPL. 1 (19-25).
Refs: 34
ISSN: 0049-0172 CODEN: SAHRBF
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objectives: Currently, available **therapies** for managing **osteoarthritis** (OA) provide symptomatic relief. Theoretical evidence suggests that exogenous **hyaluronan** (HA) administered as an intra-**articular** injection may slow disease progression. The purpose of this review is to discuss cellular and immunologic effects of HA that could affect OA progression and to present data from a clinical trial that evaluated HA structural effects. **Methods**: The medical and scientific literature regarding the cellular, immunologic, and structural effects of HA on the joint environment and function are reviewed. Results: Cellular effects of exogenous HA that affect the joint include increasing endogenous HA synthesis, stimulating proteoglycan synthesis, and inhibiting the release of chondrodegrading enzymes. The immunologic effects of HA are inhibition of mononuclear cell phagocytosis and leukocyte migration, chemotaxis, and phagocytosis. Also, HA is a free radical scavenger. In a pilot study using arthroscopy, cartilage deterioration was less in the HA-**treated** group compared with the control group. Conclusions: Considerable evidence supports the positive effects of HA on joint cellular and immunologic function. However, further

clinical studies are needed to determine whether these effects are valuable in altering the progression of OA. (C) 2000 by W.B. Saunders Company.

L22 ANSWER 40 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2000380240 EMBASE
TITLE: Intra-**articular** sodium hyaluronate in **osteoarthritis** of the knee.
AUTHOR: Altman R.D.
CORPORATE SOURCE: Dr. R.D. Altman, Miami Veterans Affairs, Medical Center, 1201 NW 16th St, Miami, FL 33125, United States. raltman@med.miami.edu
SOURCE: Seminars in Arthritis and Rheumatism, (2000) 30/2 SUPPL. 1 (11-18).
Refs: 32
ISSN: 0049-0172 CODEN: SAHRBF
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objectives: **Hyaluronan** (HA) has recently been approved in the United States for management of pain in **osteoarthritis** (OA) of the knee and is the first biological available for use in OA. To better understand the **therapeutic** role of HA, this review focuses on comparative clinical trial data. **Methods**: Literature reports of clinical trials comparing HA with placebo, non-steroidal anti-**inflammatory** drugs, and intra-**articular** corticosteroids were reviewed. The pivotal US trial evaluating HA efficacy and safety was summarized. Results: Over the past decade, 5 of 8 controlled clinical trials demonstrated HA was superior to placebo in relieving the pain of OA. A sixth trial showed improvement in a subset of older patients with more severe disease. Comparison of HA with corticosteroids showed equal pain relief in the first few weeks after **therapy**, with HA demonstrating more sustained benefit up to 60 days. In the recent US trial, HA was statistically superior to placebo and at least as effective as naproxen in providing analgesia. In all trials reporting adverse effects, the primary adverse effect with HA was pain at the injection site. Conclusions: HA appears effective in relieving the pain of OA of the knee and provides a relatively safe alternative for patients for whom conventional **therapy** has failed. (C) 2000 by W.B. Saunders Company.

L22 ANSWER 41 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1999424806 EMBASE
TITLE: Scintigraphic evaluation of dogs with acute **synovitis** after **treatment** with glucosamine hydrochloride and **chondroitin sulfate**.
AUTHOR: Canapp S.O. Jr.; McLaughlin R.M. Jr.; Hoskinson J.J.; Rousch J.K.; Butine M.D.
CORPORATE SOURCE: Dr. S.O. Canapp Jr., Dept. of Veterinary Medicine/Surgery, College of Veterinary Medicine, University of Missouri-Columbia, Columbia, MO 65211, United States
SOURCE: American Journal of Veterinary Research, (1999) 60/12 (1552-1557).

Refs: 41
ISSN: 0002-9645 CODEN: AJVRAH
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 023 Nuclear Medicine
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objective - To evaluate the effects of orally administered glucosamine hydrochloride (GlAm)-**chondroitin sulfate** (CS) and GlAm-CS-S-adenosyl-L- methionine (SAMe) on chemically induced **synovitis** in the radiocarpal joint of dogs. Animals - 32 adult mixed-breed dogs. **Procedure** - For 21 days, all dogs received a sham capsule (3 groups) or GlAm-CS (prior **treatment** group) in a double-blinded study. Unilateral carpal **synovitis** was induced by injecting the right radiocarpal joint with chymopapain and the left radiocarpal joint (control joint) with saline (0.9% NaCl) solution. Joints were injected on alternate days for 3 injections. After induction of **synovitis**, 2 groups receiving sham **treatment** were given GlAm-CS or GlAm-CS-SAMe. Another group continued to receive sham capsules (control group). Joint **inflammation** was quantified, using nuclear scintigraphy, before injection of joints and days 13, 20, 27, 34, 41, and 48 after injection. Lameness evaluations were performed daily. Results - Dogs given GlAm-CS before induction of **synovitis** had significantly less scintigraphic activity in the soft-tissue phase 48 days after joint injection, significantly less uptake in the bone phase 41 and 48 days after joint injection, and significantly lower lameness scores on days 12 to 19, 23, and 24 after injection, compared with other groups. Conclusions and Clinical Relevance - Analysis of results of this study suggest that prior **treatment** with GlAm-CS for 21 days had a protective effect against chemically induced **synovitis** and associated bone remodelling. Prior **treatment** with GlAm-CS also reduced lameness in dogs with induced **synovitis**.

L22 ANSWER 42 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1999375484 EMBASE
TITLE: [The clinical and experimental use of hyaluronic acid in the **therapy** of gonarthrosis: A review]. UBERSICHT UBER DIE KLINISCHE UND EXPERIMENTELLE ANWENDUNG DER HYALURONSAURE BEI GONARTHROSE.
AUTHOR: Stove J.; Puhl W.
CORPORATE SOURCE: Dr. J. Stove, Orthop. Abteil. Rehab. Krankhs. Ulm, Orthop. Klin. Querschnittgelahmtenz., Universitat Ulm, Oberer Eselsberg 45, D-89081 Ulm, Germany
SOURCE: Zeitschrift fur Orthopadie und Ihre Grenzgebiete, (1999) 137/5 (393-399).
Refs: 50
ISSN: 0044-3220 CODEN: ZOIGAP
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 031 Arthritis and Rheumatism
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: German
SUMMARY LANGUAGE: English; German
AB Aim: The aim of this survey is to review the clinical and experimental background for the use of **hyaluronan** (HA) in the **therapy**

of gonarthrosis. Materials and **methods**: Clinical and experimental studies were analysed following a medline literature-research. To determine the clinical efficiency of HA only randomized and controlled studies were taken into account. As a result of this analysis the current knowledge for the clinical and experimental use of HA is portrayed. Results: Numerous controlled, randomized studies showed beneficial effects for pain relief and joint function after i.art. injection with HA. Placebo, NSAIDs and steroids were used as control medications. The effect of HA was significantly better compared to placebo, and similar or superior in comparison to other verums (NSAIDs, steroids). After completion of HA-**therapy** a long lasting effect compared to steroids was shown. Review of the literature reveals side-effect rates for HA-**therapy** similar to those for placebos. In various experimental studies a clear working mechanism could not be identified, especially reasons for the long lasting effects are still unknown. However, some studies showed an anti- **inflammatory** effect in **inflamed** joints and in stimulated culture-conditions. A stimulating effect of the HA-production by synoviocytes after administration of HA was shown. Further studies will have to demonstrate the cellular effects in vitro and in animal models in detail. Conclusion: HA is therefore classified as a 'symptom slow acting drug for **osteoarthritis**' because a 'structure-modifying (chondroprotective) effect' has not been proven yet.

L22 ANSWER 43 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1998414573 EMBASE
TITLE: Effects of intra-**articular** injections of sodium hyaluronate (orthovisc) and betamethasone on **osteoarthritis** of the knee.
AUTHOR: Tekeoglu I.; Adak B.; Goksoy T.; Tosun N.
CORPORATE SOURCE: Dr. I. Tekeoglu, Dept. Phys. Medicine/Rehabilitation, Faculty of Medicine, Yuzuncu Yil University, Van, Turkey
SOURCE: Journal of Rheumatology and Medical Rehabilitation, (1998) 9/4 (220-224).
Refs: 15
ISSN: 1300-0691 CODEN: RTRDEC
COUNTRY: Turkey
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 019 Rehabilitation and Physical Medicine
031 Arthritis and Rheumatism
033 Orthopedic Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; Turkish

AB The purpose of this study was to compare the efficacy and tolerability of intra-**articular** injections of 20 mg of Sodium Hyaluronate and 3 mg- betamethasone in an open randomized trial. 40 patients with **gonarthritis** were randomly allocated in 2 different groups of 20 people. All subjects included in the groups were female with mean age of 57.84 57.84±5.66 and 58.26±6.05 years. Intra-**articular** injections were administered once a week for three weeks. All patients suffering from **inflammatory** knee **osteoarthritis** were examined prior to and after the study. Efficacy rates of the two **treatment methods** during subsequent examinations in the 3(rd) and 15(th) weeks were noted. WOMAC assessment, Visual Analogue Scale, clinical severity and radiological severity according to Kellgren Lawrance index were also assessed in both groups. Both medications were well tolerated with no complications. Results in the 3(rd) week were in favour of betamethasone group. However there were clinically significant

difference in favour of Sodium Hyaluronate (Orhovisc) **treatment** group on the 15(th) week. According to results of 15 week follow-up study comparing the efficacy and tolerability rates between Sodium Hyaluronate and Betamethasone, Hyaluronate injection could be more effective in **osteoarthritis** on the long term basis.

L22 ANSWER 44 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1998357362 EMBASE
TITLE: [Local **treatment** of **inflammatory** arthropathies: Free radical scavenging].
TERAPIA INTRA-ARTICOLARE NELLE ARTROPATIE INFIAMMATORIE: LO SCAVENGING CON ANTIOSSIDANTI.
AUTHOR: Lapadula G.; Iannone F.; Pipitone V.
CORPORATE SOURCE: G. Lapadula, Dipto. Medicina Interna Lavoro, Sezione di Reumatologia, Universita degli Studi di Bari, Bari, Italy
SOURCE: Reumatismo, (1998) 50/1 (1-4).
Refs: 32
ISSN: 0048-7449 CODEN: REUMEH
COUNTRY: Italy
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 026 Immunology, Serology and Transplantation
031 Arthritis and Rheumatism
033 Orthopedic Surgery
037 Drug Literature Index
LANGUAGE: Italian

L22 ANSWER 45 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1998270436 EMBASE
TITLE: Intra-**articular** hyaluronic acid in the **treatment** of **osteoarthritis** of the knee: Clinical and morphological study.
AUTHOR: Frizziero L.; Govoni E.; Bacchini P.
CORPORATE SOURCE: L. Frizziero, Divisione di Medicina Interna, Ospedale Maggiore, Largo B. Nigrisoli 2, 40133 Bologna, Italy
SOURCE: Clinical and Experimental Rheumatology, (1998) 16/4 (441-449).
Refs: 39
ISSN: 0392-856X CODEN: CERHDP
COUNTRY: Italy
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objective: To evaluate, in a pilot, open clinical trial on 40 patients with knee **osteoarthritis**, the structural changes in the **synovial membrane** and cartilage following **treatment** with intra-**articular** hyaluronic acid (HA-Hyalgan®). **Methods**: The structural effects of HA given as 5 weekly injections (20 mg/2 ml once a week for 5 weeks), were evaluated by microarthroscopy and morphological analysis of biopsy samples taken at baseline and after 6 months, under blind conditions. Clinical efficacy was also evaluated using visual analogue scales for pain and functional parameters. Results: At 6 months, the microarthroscopic evaluation indicated that the majority of the patients (60%) showed no changes compared to baseline, while 32.5% of the patients showed improvement in the grading and/or extension of cartilage lesions and 7.5% showed a

worsened condition. These changes were accompanied by a statistically significant reduction in the synovial **inflammation** (p = 0.001). The results were confirmed by morphological examination of the cartilage and **synovial membrane**. At 6 months compared to baseline, a statistically significant reconstitution of the superficial amorphous layer of the cartilage (p = 0.0039), an improvement in the chondrocyte density (p = 0.0023) and vitality (p = 0.05), and a statistically significant reduction in synovial **inflammation** (p = 0.0001) accompanied by a significant increase in the synovial repair process (p = 0.0001) were observed. Significant and long lasting improvement in pain and joint mobility were also seen after HA **treatment**. Joint effusion, when present, was reduced. The **treatment** was well tolerated. Conclusion: Hyalgan® represents a useful **therapy** for knee OA, with long-lasting symptomatic efficacy and potential positive effects on joint tissues. Other studies, in **particular** placebo-controlled studies, are warranted to confirm these promising results observed on joint tissues.

L22 ANSWER 46 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 96039611 EMBASE
DOCUMENT NUMBER: 1996039611
TITLE: The role of viscosupplementation with hylan G-F 20 (Synvisc®) in the **treatment** of **osteoarthritis** of the knee: A Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-**inflammatory** drugs (NSAIDs) and NSAIDs alone.
AUTHOR: Adams M.E.; Atkinson M.H.; Lussier A.J.; Schulz J.; Siminovitch K.A.; Wade J.P.; Zummer M.
CORPORATE SOURCE: Department of Medicine, University of Calgary, 3330 Hospital Drive NW,Calgary, Alta. T2N 4N1, Canada
SOURCE: Osteoarthritis and Cartilage, (1995) 3/4 (213-225). ISSN: 1063-4584 CODEN: OSCAEO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 031 Arthritis and Rheumatism
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB To determine the safety and efficacy of viscosupplementation with hylan G-F 20, a cross-linked **hyaluronan** preparation used either alone or in combination with continuous non-steroidal anti-**inflammatory** drug (NSAID) **therapy**, a randomized, controlled, multicenter clinical trial, assessed by a blinded assessor, was conducted in 102 patients with **osteoarthritis** (OA) of the knee. All patients were on continuous NSAID **therapy** for at least 30 days prior to entering the study. Patients were randomized into three parallel groups: (1) NSAID continuation plus three control arthrocenteses at weekly intervals; (2) NSAID discontinuation but with three weekly intra-**articular** injections of hylan G-F 20; and (3) NSAID continuation plus three injections, one every week, intra-**articular** injections of hylan G-F 20. Outcome measures of pain and joint function were evaluated by both the patients and an evaluator at baseline and weeks 1, 2, 3, 7 and 12, with a follow-up telephone evaluation at 26 weeks. At 12 weeks all groups showed statistically significant improvements from baseline, but did not differ from each other. A statistical test for equivalence, the q-statistic, demonstrated that viscosupplementation with hylan G-F 20 was at least as good or better than continuous NSAID

therapy for all outcome measurements except activity restriction. At 26 weeks both groups receiving hylan G-F 20 were significantly better than the group receiving NSAIDs alone. A transient local reaction was observed in three patients after hylan G-F 20 injection; only one patient withdrew from the study as a result and all recovered without any sequela. Hylan G-F 20 is a safe and effective **treatment** for OA of the knee and can be used either as a replacement for or an adjunct to NSAID **therapy**.

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ACCESSION NUMBER: 94134874 EMBASE
DOCUMENT NUMBER: 1994134874
TITLE: Viscosupplementation of osteoarthritic knees with hylan: A **treatment** schedule study.
AUTHOR: Scale D.; Wobig L.M.; Wolpert W.
CORPORATE SOURCE: Biomatrix Inc, 65 Railroad Avenue,Ridgefield, NJ 07657, United States
SOURCE: Current Therapeutic Research - Clinical and Experimental, (1994) 55/3 (220-232).
ISSN: 0011-393X CODEN: CTCEA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 031 Arthritis and Rheumatism
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Double-blind, randomized, 12-week studies, which included 6-month follow-up, were conducted to compare the efficacy and safety of hylan versus physiologic saline administered intra-**articularly** to the affected joint of 80 patients with degenerative **osteoarthritis** of the knee. During a 2-week preinjection washout period and for the duration of the studies, patients received no steroidal or nonsteroidal anti-**inflammatory** drugs or analgesic medication. Two intra-**articular** injections administered 2 weeks apart were compared with three intra-**articular** injections given 1 week apart. Outcome measures included pain under weight-bearing movement, pain at night, reduction of activity while performing daily tasks, improvement of the most painful knee movement, and overall evaluation of **therapeutic** efficacy. Most parameters were evaluated by both the patient and the investigator. Compared with the control group, the two-injection and three-injection hylan **treatment** groups both showed statistically significantly greater improvement for the pain outcome measures as well as overall evaluation of **treatment** at the 12-week evaluation. The three-injection group showed statistically significantly greater improvement for all outcome measures compared with the two-injection group at the 12-week evaluation. At the 6-month follow-up, results in both hylan **treatment** groups were significantly superior to those in the control group in terms of reducing weight-bearing pain and night pain and restoring joint function. No generalized adverse events were observed, and only one local, transient adverse event (muscle pain) was reported. The results suggest that hylan is an extremely effective and safe viscosupplementation **therapy** for the management of degenerative **osteoarthritis** of the knee. Beneficial results can be maximized using a **treatment** schedule of three hylan injections administered at 1-week intervals.

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on STN
ACCESSION NUMBER: 94096368 EMBASE
DOCUMENT NUMBER: 1994096368
TITLE: Hyaluronic acid. A review of its pharmacology and use as a surgical aid in ophthalmology, and its **therapeutic** potential in joint disease and wound healing.
AUTHOR: Goa K.L.; Benfield P.
CORPORATE SOURCE: Adis International Limited, 41 Centorian Drive,Mairangi Bay, Auckland 10, New Zealand
SOURCE: Drugs, (1994) 47/3 (536-566).
ISSN: 0012-6667 CODEN: DRUGAY
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 012 Ophthalmology
030 Pharmacology
031 Arthritis and Rheumatism
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Hyaluronic acid is a naturally occurring polysaccharide with distinct physicochemical properties which underlie its application as a viscoelastic tool in ophthalmological surgery. In cataract surgery the role of hyaluronic acid in facilitating **procedures** and protecting the corneal endothelium is well established. Some benefit was also been gained with the use of hyaluronic acid in penetrating keratoplasty trabeculectomy retinal reattachment and trauma surgery although its efficacy in these indications is less well-defined in the published literature. In addition to its lubricating and cushioning properties demonstration of some in vitro anti-**inflammatory** activity and a possible disease-modifying effect for hyaluronic acid in animals has prompted its investigation as a **treatment** in **osteoarthritis** and to a much lesser extent in rheumatoid **arthritis**. Hyaluronic acid 20mg as weekly intra-**articular** injections for 3 to 7 weeks improved knee pain and joint motion in patients with **osteoarthritis**. Although this occurred to a greater degree than with placebo in most comparisons the effects of hyaluronic acid was similar to those of placebo in the largest trial. In the few available comparisons with other agents hyaluronic acid appeared equivalent to methylprednisolone 40mg (for 3 weeks) and to a single injection of triamcinolone 40mg. Hyaluronic acid was distinguished from other **therapies** by providing a sustained effect after **treatment** discontinuation. Together with its very good tolerability profile these properties justify further study of hyaluronic acid in patients with **osteoarthritis**. Some limited evidence of improvement in patients with rheumatoid **arthritis** and a possible healing effect of hyaluronic acid on tympanic membrane perforations represent additional areas of interest for future investigation. In summary hyaluronic acid is a well-established adjunct to cataract surgery and may prove to be a promising option in the **treatment** of patients with **osteoarthritis**. Its very good tolerability provides further impetus for examination of its potential role in on extended scope of arthritic and ophthalmological indications and in wound healing.

L22 ANSWER 49 OF 49 JICST-EPlus COPYRIGHT 2004 JST on STN
ACCESSION NUMBER: 1000171587 JICST-EPlus
TITLE: Effects of **Hyaluronan** Fragments on Synovial Fibroblasts in Rheumatoid **Arthritis**.

AUTHOR: SAKAI T; KAMBE F; SEO H
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CORPORATE SOURCE: Nagoya Univ., Nagoya, Jpn
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SOURCE: Environ Med, (1999) vol. 43, no. 2, pp. 95-97. Journal Code: G0447A (Fig. 1, Ref. 10)
ISSN: 0287-0517
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Short Communication
LANGUAGE: English
STATUS: New
AB **Intraarticular** injection of **hyaluronan** (HA) is an effective **treatment** of **inflammatory** joint diseases. However, little is known about the mechanisms of this HA effect. HA is a polysaccharide consisting of unbranched repeats of disaccharide units, and its molecular weight is distributed in the range of 40kDa to 60,000kDa in the synovial fluid of patients with rheumatoid **arthritis** (RA) and other arthropathies. To elucidate the anti-**inflammatory** action of HA, we investigated the effects of three different sizes of HA fragments (200kDa, 940kDa and 2100kDa) on tumor necrosis factor (TNF)-A-dependent production of interleukin (IL)-8 by synovial fibroblasts obtained from RA patients. The cells derived from three different patients were **treated** with 1mg/ml of each HA fragment for 20h, and then stimulated with TNF-A for 10h. IL-8 in culture media were measured by enzyme-linked immunosorbent assay. HA 200kDa had only marginal effects on IL-8 production. However, **treatment** with HA 940kDa or HA 2100kDa resulted in a significant decrease in IL-8 production. Similar results were obtained from three different cells, although the extent of the decrease in IL-8 varied among the cells. These results suggested that high-molecular weight HA has an inhibitory effects on TNF-A-dependent production of IL-8 in synovial fibroblasts. (author abst.)

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               E MARCUM FRANK/AU
               E MARCUM F/AU

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L1             1 SEA ABB=ON  "CHONDROITIN SULFATE"/CN
               E CS4 CHONDROITIN SULFATE/CN
               E N-ACETYL D-GLUCOSAMINE/CN
               E N-ACETYL-D-GLUCOSAMINE/CN
L2             1 SEA ABB=ON  N-ACETYL-D-GLUCOSAMINE/CN
               E HYALURONAN/CN
L3             1 SEA ABB=ON  HYALURONAN/CN
L4           292 SEA ABB=ON  L1 OR L2 OR L3 OR ?CHONDROITIN?(W)?SULFATE? OR
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                 ?GLUCOSAMINE? OR ?HYALURONAN?

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                 ?GLUCOSAMINE? OR ?HYALURONAN?
L6             0 SEA ABB=ON  L5 AND ?ARTICUL?(W)?CARTILAG?(4A)?DIATHROD?(W)?JOIN
                 T?
L7             0 SEA ABB=ON  L5 AND ?CARTILAG?(4A)?DIATHROD?(W)?JOINT?
L8           188 SEA ABB=ON  L5 AND ?CARTILAG?(4A)?JOINT?
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L10            0 SEA ABB=ON  L9 AND ?DIATHROD?
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L12          893 SEA ABB=ON  L7 OR L11
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